Ambiguous Genitalia, Two Decades of Experience: Clinical Management and Sex Assignment

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Abstract

Objective
Ambiguous genitalia constitute a major social and medical emergency. This study was conducted to assess the relevant clinical significance of this important clinical entity.

Methods
During the period 1989-2008, eighty-one patients with ambiguous genitalia were evaluated in a Pediatric Endocrine Clinic at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia.

Results
Of these 53 (65.4%) were genetically females (46XX), and 28 (34.6%) were having a male genetic sex (46XY). The majority of them were proven to have congenital adrenal hyperplasia. Twenty-five (47.2%) of the genetic females were wrongly assigned a male sex due to severe virilization while only two (7.1%) of the genetic males were wrongly assigned as females. Although early neonatal diagnosis facilitates appropriate management, sociocultural factors such as a bias concerning the male gender in the community and strong influence of the grandparents constitute major management obstacle. All genetic males who were wrongly assigned as females accepted re-assignment, and four (16%) of the 25 genetic females who were wrongly assigned as males refused re-assignment.

Conclusion
A team approach is mandatory for successful management. Guidelines for approaching the problems are also highlighted.

Keywords: ambiguous, genitalia, children, Saudi Arabia, management, sex-assignment

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Introduction

Ambiguous genitalia, currently known as disorders of sex development (DSD) in a newborn is not that uncommon in our community, due to increased prevalence of consanguineous matings and multiple siblings in the one family. Not only might there be immediate physiological problems such as shock, hypoglycaemia or subsequent salt loss, but there is also a need to assign a sex. Failure to do so can lead to wrong sex assignment with grave consequences.

In this report the author presents his own experience over two decades (1989-2008) with ambiguous genitalia, focusing on the clinical management and sex rearing at a Pediatric Endocrine Clinic, King Khalid University Hospital (KKUH), Riyadh, Central province, Saudi Arabia. The KKUH is the main teaching hospital of the King Saud University (KSU) and considered as one of the major referral hospitals in the region, and provides primary, secondary, and tertiary health care services for the local population and also receives patients referred from all over the country.

Materials and Methods

Eighty-one newborns and children with ambiguous genitalia were managed by the author in the period under review (1989-2008). Parents were interviewed, in addition to medical records review. Data obtained including age and sex at presentation, relevant family and social history, giving a special consideration to level of parent’s education, satisfaction regarding management and knowledge given, pregnancy, clinical manifestations and results of all the laboratory, radiological and ancillary investigations. The degree of severity of virilization of the female external genitalia was classified as suggested by Prader’s classification. Genetic sex was based on chromosomal studies done on lymphocytes. Pelvic ultrasonography, genitography, and other definitive etiological diagnosis was based on detailed and specific hormonal investigations as recommended.

At the time of initial presentation, the sexual ambiguity issue is discussed openly and in details, including the future expectation, with parents, and grandparents if needed. The current Islamic guidelines for sex assignment were also discussed. The opinions of Islamic ulama leaders, at times, were needed. A multi-disciplinary team constitutes of a pediatric endocrinologist, pediatric surgeon, urologist, plastic surgeon, geneticist and psychologist or pediatric psychiatrist was involved in the discussions and decision making. A period of time is given for the parents to think and decide. If the parents were in agreement, the appropriate name and a legal certificate is issued to be presented to the concerned civil services, and the next steps (i.e. medical and surgical plans) are outlined. However, if no agreement was reached discussion was continued on an outpatients setting. The corrective surgery is performed before 18 months of age, i.e., before the child develops gender awareness.

Regular routine clinic visits were scheduled every three months for the first 2-3 years, and every six months thereafter, to ensure compliance and answer any question arises. Continuous counselling and psychological support is continued, as well as updated information to the parents and disclosing information to the patient when appropriate.

Results

The various clinical characteristics of all patients are shown in Tables 1 and 2. Their age, at the time of presentation, ranged between one day to eight years. Fifty-three (65.4%) patients were genetic females (46XX), while twenty-eight (34.6%) were having a male genetic sex (46XY). The majority of them were proven to have congenital adrenal hyperplasia. Twenty-five (47.2%) of the genetic females patients were wrongly assigned as a male sex due to severe virilization.
<table>
<thead>
<tr>
<th>Final diagnosis (No. of patients)</th>
<th>Given sex (No.)</th>
<th>Clinical Presentation</th>
<th>Prader’s Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P1</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia (51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 hydroxylase deficiency (41)</td>
<td>M (21) F (12) UD (8)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>11 hydroxylase deficiency (9)</td>
<td>M (4) F (4) UD (1)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>3 hydroxyysteroid dehydrogenase deficiency (1)</td>
<td>F (1)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Isolated clitoral hypertrophy (2)</td>
<td>F (2)</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

M=male; F=female; UD=undetermined; (+) positive; (-) negative
Table 2: Clinical data of 28 patients with 46 XY genetic sex with ambiguous genitalia

<table>
<thead>
<tr>
<th>Final diagnosis (No. of patients)</th>
<th>Given sex (No.)</th>
<th>Clinical presentation</th>
<th>Hyper pigmentation</th>
<th>Salt wasting</th>
<th>Family history of similar disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital adrenal hyperplasia 3β-HSD def (2)</td>
<td>M (2) F (0) UD (0)</td>
<td>P 3-4</td>
<td>+ (2)</td>
<td>+ (2)</td>
<td>+ (2)</td>
</tr>
<tr>
<td>5-α-reductase deficiency (4)</td>
<td>M (1) F (2) UD (1)</td>
<td>Severe hypospadias with coronal Bilateral or unilateral undescended testicle</td>
<td>-(4)</td>
<td>-(4)</td>
<td>-(3)</td>
</tr>
<tr>
<td>Partial androgen insensitivity (3)</td>
<td>M (3) F (0) UD (1)</td>
<td>Severe hypospadias Bilateral or unilateral undescended testicle</td>
<td>-(3)</td>
<td>-(3)</td>
<td>-(2)</td>
</tr>
<tr>
<td>Complete androgen insensitivity (4)</td>
<td>M (0) F (1) UD (3)</td>
<td>Normal female external genitalia</td>
<td>-(4)</td>
<td>-(4)</td>
<td>+(4)</td>
</tr>
<tr>
<td>Hypogonadotrophin (4)</td>
<td>M (4) F (0) UD (0)</td>
<td>Micropenis, hypoplastic scrotum, unilateral or bilateral undescended testicle</td>
<td>-(4)</td>
<td>-(4)</td>
<td>-(4)</td>
</tr>
<tr>
<td>Multiple congenital anomalies (9)</td>
<td>M (8) F (0) UD (1)</td>
<td>Multiple congenital anomalies, bifid scrotum, unilateral or bilateral undescended testicle, hypospadias with coronal</td>
<td>-(9)</td>
<td>-(9)</td>
<td>+(2)</td>
</tr>
<tr>
<td>Local anorectal anomalies (2)</td>
<td>M (2) F (0) UD (0)</td>
<td>Anal atresia, bifid scrotum hypospadias, unilateral undescended testicle</td>
<td>-(2)</td>
<td>-(2)</td>
<td>-(2)</td>
</tr>
</tbody>
</table>

(M) Male, (F) Female, (UD) Undetermined, Prader’s classification (P)
Although, early neonatal diagnosis and clear counseling will facilitate appropriate management, socio-cultural factors such as a bias concerning the male gender in the community and pressures from grandparents constitute a major management obstacle. In four patients from three families, presented in the neonatal period parents refused sex-reassignment as dictated by the grandparents which constitutes a major socio-cultural pressure, in spite of, their high educational level (high school and university) and the presence of other male siblings. One child died at the age of 14 with sepsis while another one underwent a surgical procedure, outside the country, were the uterus and ovaries removed. Two patients who were diagnosed at the neonatal period to have congenital adrenal hyperplasia due to 21 hydroxylase deficiency, and refused sex re-assignment were referred at 6 and 8 years of age for second opinion upon their request. They claimed lack of appropriate information. Sex re-assignment was accepted after the appropriate counselling and psychological preparation and indicates the importance of team approach in such conditions. Two male siblings with 5-α-reductase deficiency were incorrectly assigned by a general practitioner a female sex, without any investigations, and even, he told parents that gender will be clarified more at puberty. This was correctly re-assigned at 7 and 12 years of age. A female with salt loosing 21 hydroxylase deficiency, congenital adrenal hyperplasia, who was assigned as a female sex to start with, was able to conceive and delivered by caesarian section a normal girl.

Discussion

parents what they will do depends on the diagnosis and given sex.\textsuperscript{1,2,21,22} As important as, understanding the medical aspect of the disorder, it is essential to know the current Islamic recommendations put forward by the senior ulama council in Saudi Arabia,\textsuperscript{5} and therefore should be outlined. These recommendations are translated as follows: 1) A sex-change operation, i.e., converting a completely developed gender to opposite sex, is totally prohibited. It is considered criminal. This is clearly supported by the holy Koran and the prophet’s sayings. 2) Those who have both male and female organs need to be investigated and if the evidence is more into
a male, it is then permissible to treat him medically (by hormones or surgery), to eliminate his ambiguity, and raise him male. If the evidence is more into a female, it is permissible to treat her medically (by hormones or surgery) to eliminate her ambiguity, and raise her as a female. 3) Physicians must explain the results of medical investigations to the child’s guardian (be it a male or a female) so they may be well informed.

A diversity of causes led to sexual ambiguity in our series, with congenital adrenal hyperplasia and its various virilizing forms being the commonest. This high occurrence is a reflection of multiple siblings involvement of a common autosomal recessive disorder in our community.6,7 Saedi-Wong et al8 showed earlier a high rate of parity and consanguineous mating among the Saudi population.

Genetic females (46XX) with normal ovaries, and internal female organs (uterus, fallopian tubes, and upper vagina) with variable degrees of virilization of the external genitalia usually have congenital adrenal hyperplasia and should be raised as females, not only due to the ease of reconstruction of the external genitalia,21,22 but also because of high fertility rate and child-bearing as adults.24 The surgery generally should be performed early before the child develops gender awareness. The techniques used for clitoral recession and vaginoplasty are continually improving.23 However, in contrast to this, a child with a sexual ambiguity and an XY chromosomes, creates a rather more difficult and challenging problem not only to the child and his family, but also to the healthcare giver. Although, familial interactions with the young child during the first months of life are key factors in gender and sexual role development, the future penile size and potential for penile growth in relation to sexual function, at a level that can be expected to be satisfactory, is still unpredictable. Also, it is important to understand that it is more difficult to reconstruct a penis rather than create a vagina.21,23 Also, the dominating role of the male gender in the community, should not over rule the Islamic Laws which should not be ignored and given a prime consideration. The psychological and social stigma strengthened by pressures from the grandparents should not be overlooked.

A bias concerning the influence of the karyotype such as the perception that a child with XY genotype should be raised as a male is not correct. Patients with complete end organ unresponsiveness (insensitivity syndrome) should be raised as females, while in partial forms the decision will be based on the degree of response to trials of exogenous androgen. In those who demonstrated appreciable response to a trial of exogenous testosterone should be raised as males, as they achieve a remarkable degree of masculinization at puberty. This is also the case in 5-α-reductase deficiency, many of them will be fertile as adults.25,26

In conclusion, sexual ambiguity is not that uncommon in our community due to a high rate of consanguineous matings and multiple siblings involvement. A diversity of causes has been noted, with congenital adrenal hyperplasia being the commonest. Late diagnosis and various socio-cultural factors have negative impacts on management in particular wrong sex assignment and its consequences. Increased awareness, detailed history, careful physical examination coupled with the appropriate and necessary laboratory and radiological investigation aid the early diagnosis. An experienced team is mandatory for successful management.

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