Clinical Review of 95 Patients with 46,XX Disorders of Sex Development Based on the New Chicago Classification

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ABSTRACT

Study Objective: The aim of our study was to determine the etiologic distribution of 46,XX disorder of sexual development (DSD) according to the new DSD classification system and to evaluate the clinical features of this DSD subgroup in our patient cohort.

Participants: The evaluation criteria and clinical findings of 95 46,XX patients were described by clinical presentation, gonadal morphology, genital anatomy, associated dysmorphic features, presence during prenatal period with/without postnatal virilization, hormonal characteristics, and presence or absence of steriodogenic defects among 319 patients with DSD.

Results: Types and ratios of each presentation of our 95 patients with 46,XX DSD were as follows: 82 had androgen excess (86.3%); (74 had classical congenital adrenal hyperplasia, 2 had CAH variant possibility of P450-oxidoreductase gene defect), 6 had disorders of ovarian development (6.3%); (1 patient had gonadal dysgenesis with virilization at birth with bilateral streak gonad, 4 patients had complete gonadal dysgenesis, and 1 patient had ovotesticular DSD) and 7 had other 46,XX DSD. Two sisters, who had 46,XX complete gonadal dysgenesis, were diagnosed with Perrault Syndrome with ovarian failure due to streak gonads and associated with sensorineural deafness. 46,XX DSD are usually derived from intrauterine virilization and CAH is the most common cause of 46,XX DSD due to fetal androgen exposure.

Key Words: Disorders of sex development, 46,XX karyotype, Etiology

Introduction

Formerly, intersex patients could be subdivided into three main groups: disorders associated with gonadal dysgenesis, disorders associated with undervirilization of 46,XY individuals, and disorders associated with prenatal virilization of 46,XX subjects. Changes in nomenclature and classification were recently proposed in order to incorporate genetic advances and substitute gender-based diagnostic labels in terminology. The Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology consensus group proposed the new Chicago classification of “Disorders of sex development” (DSD) into: Sex Chromosome DSD (45,X Turner and variants, 47,XXY Klinefelter and variants, 45X/46XY Mixed gonadal dysgenesis), and Chromosomal Ovotesticular DSD (46XX/46XY chimeric or mosaic type); 46,XY DSD (Disorders of Testicular Development or Disorders in Androgen Synthesis/Action); and 46,XX DSD (Disorders of Ovarian Development or Fetal Androgen Excess) (Table 1).1-3 In this classification, the former term “female pseudohermaphrodite” which has been used to describe patients with 46,XX karyotype and masculinized external genitalia, was replaced by the term of 46,XX DSD.

46,XX DSD can result from fetal androgen excess, disorders of ovarian development, or other 46,XX DSD. Although some series reported before the Chicago classification, there are few data describing 46,XX DSD group of patients.4-7 The aims of our study were to (1) describe the evaluation criteria, (2) describe the series of patients according to the new DSD classification, and (3) discuss the results, including (4) extensive discussion of several less commonly occurring causes in our patient cohort.

Materials and Methods

We retrospectively reviewed the records of patients who were diagnosed within the past 20 years. Ninety-five patients (29.8%) out of 319 with DSD, who were admitted to the Pediatric Endocrinology Clinic between December 1992 and December 2012, were diagnosed with 46,XX DSD. All patients of Dr. Gö were evaluated. Patients’ ages ranged from newborn to 23 years (mean: 2.8 ± 4.3 years). Duration of follow-up of patients was 5.5 ± 4.1 years. Patients’ prenatal and maternal history, genital phenotypic appearance, presence during prenatal period with/without postnatal virilization, general physical examination with attention to any associated dysmorphic features, karyotypes, ultrasonographic findings of their gonads and Mullerian structures, hormonal activity of steroidogenesis and associated disorders, and sex of rearing were evaluated. The degree of
external genital virilization was determined by using the Prader classification. Chromosomal analysis were done by examining metaphase G bands prepared from peripheral blood lymphocytes. Internal genital structures were assessed by ultrasonographic or radiologic imaging and by laparotomy when considered necessary.

If the patient had no palpable gonads and had 46,XX karyotype with the presence of bilateral ovary, a congenital adrenal hyperplasia (CAH) screen was ordered to all patients. Blood lymphocytes. Internal genital structures were examined metaphase G bands prepared from peripheral

Table 1
Chicago Classification of Causes of Disorders of Sex Development (DSDs)

<table>
<thead>
<tr>
<th>Sex chromosome</th>
<th>46, XY DSD</th>
<th>46,XX DSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. 47,XY (Klinefelter syndrome and variants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. 45X (Turner syndrome and variants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. 45X/46 XY (Mixed gonadal dysgenesis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. 46,XX/46 XY (chimerism)</td>
<td></td>
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</tbody>
</table>

Fig. 1 shows the step-by-step diagnostic approach used for 46,XX DSD in accordance with the new classification.

Gender assignments were approved by the local ethics committee. The ethics committee consisted of a pediatric endocrinologist, an adult endocrinologist, a pediatric surgeon, a medical geneticist, a child psychiatrist, an urologist, a gynecologist, and a forensic medicine specialist. Gender assessment teams of our university utilized multidisciplinary approach towards diagnosis, genetic counseling, medical and surgical treatment, and psychosocial support of our patients with DSD.

Results

Among the 319 patients, 95 patients had 46,XX DSD, 140 patients had 46,XY DSD, and the remaining 84 patients had sex chromosome DSD.

The types and ratios of each presentation of our 95 patients with 46,XX DSD were as follows: 82 have androgen excess (86.3%): 76 had classical CAH, 6 had disorders of ovarian development (6.3%); 1 had ovotesticular DSD, 5 had disorders of androgen action (5.2%); 2 had adrenal hyperplasia (CAH) screen was ordered to all patients. Blood lymphocytes. Internal genital structures were examined metaphase G bands prepared from peripheral

Patients were diagnosed with 46,XX gonadal dysgenesis in the presence of bilateral streak gonads (gonadal dysgenesis). The presence of both ovarian and testicular tissues in a patient was described as 46,XX ovotesticular DSD. Mullerian structures abnormalities such as Rokitansky-Mayer-Kister-Hauser syndrome (RMKHS) and cloacal abnormalities were evaluated under the group of “other 46,XX DSD.”
In CAH patients, 55 patients could be evaluated for 21OH gene mutation, and the results of analysis showed that the most frequent mutation was IVS2-13A/C (28.5%), followed by a large gene deletion (17%), Q318X (11.5%), I172N (4%), V281L (3.5%), R356W (3.5%), 8-bp (3%), complex alleles (2%), P30L (1%), and E6 cluster (1%).

Two patients (patient 1 and patient 2) with steroidogenic disorders (apparent combined P450C17 and P450C21 deficiency) had prenatal virilization without worsening of postnatal virilization suggested POR deficiency (Table 4). One of them also had 21-hydroxylase gene mutation (IVS2-656A/C), in spite of absence of postnatal virilization with low levels of adrenal androgen.

Six patients with 46,XX DSD showed the characteristics of non-CAH virilization (1 patient probably had aromatase deficiency with hypergonadotropic hypogonadism, multicystic ovaries, and maternal virilization during pregnancy: 5 had idiopathic virilism, of which 1 had genital virilization with a complex of multiple anomalies resembling Frasier Syndrome).

Within the six 46,XX patients with disorders of ovarian development, 1 had gonadal dysgenesis with virilization at birth, 4 had complete gonadal dysgenesis (CGD) with unambiguous female genitalia, and 1 had ovotesticular DSD. Two sisters, who had 46,XX complete gonadal dysgenesis were diagnosed as Perrault syndrome with ovarian failure due to bilateral streak gonads and associated sensorineural deafness without blepharophimosis-ptosis-epicanthus inversus (BPES).

Caudal dysgenesis syndrome or cloacal anomaly disorders are diagnosed in three newborn with 46,XX DSD. Some additional malformations were seen in those patients. Four patients who were admitted because of primary amenorrhea were diagnosed as RMKHS. All patients with RMKHS had primary amenorrhea with normal ovarian functions.

“Gender assignment recommendation” was done in 87 of 95 patients with 46,XX DSD by the gender assessment team at our university (Table 5). Parents of eight patients refused our support for female sex for their children. Eighty-one of them were raised as females, while 6 patients with late admission and severe degree of virilization were assigned male genders.

**Discussion**

Disorders of sex development in 46,XX individuals, according to the revised nomenclature and Chicago classification, are summarized in this paper. 46,XX DSD can result in various clinical presentations, with genetic and hormonal factors playing significant roles in the development of these disorders.
mainly either from fetal androgen excess (congenital adrenal hyperplasia, aromatase deficiency, and POR deficiency) or disorders of ovarian development (ovotesticular DSD, formerly known as “true hermaphroditism,” testicular DSD, formerly known as “XX males,” and 46,XX gonadal dysgenesis). 46,XX females exposed to increased androgen intrauterine have 2 ovaries but, the patient with a disorder of ovarian development may have streak gonads, ovotestis, dysgenetic testis, or testis. In our series, patients with 46,XX DSD are consisted of a quarter of all DSD patients. Recently, similar results were also reported.

In general, virilization occurs due to androgens of fetal and maternal origins. 46,XX DSD is commonly caused by exposure to endogenous androgens during the period of organogenesis of the female fetus. Virilization of these patients occurs independent of chromosomal sex when their external genitalia are exposed to androgens during certain critical times of development. In our group, the CAH was the most common cause of 46,XX DSD due to fetal androgen exposure (76/82, 93%). CAH due to 21-hydroxylase deficiency is the most encountered etiologic factor of 46,XX DSD lead to ambiguity of the external genitalia. It was known that 21-hydroxylase deficiency accounts for approximately 90%-95% of all cases of CAH. Older studies which did not used the new classification, showed that CAH was the most common group of DSD patients with 46,XX karyotype. In another report from our country using the Chicago classification system, it was showed that 46,XX DSD patients consist of 25% (24/95) of all DSD patients, and the majority of patients (16/24) with 46,XX DSD had CAH. These results suggest that CAH remains the most common cause of ambiguous genitalia, based on the Chicago classification.

Disorders other than CAH usually constitute small groups. Patients with ovarian dysgenesis, as 6.3% of patients, comprise the second group among 46,XX DSD. Erdogan et al also reported that the 4 of 24 46,XX DSD patients had ovarian dysgenesis as consisting of second frequent group.

All patients with CAH presented with ambiguous genitalia with/without salt wasting. Seven cases had incomplete precocious puberty, 4 patients had combined precocious puberty, had nonpalpable gonads with male phenotype. The salt wasting form comprises 30% of all CAH patients. CAH is a group of autosomal recessive disorders mainly caused by defects in the steroid 21-hydroxylase (CYP21A2) gene. In our group, the most frequent mutation was IVS2-13A/C (28.5%). Generally, the characteristics of CAH patients were not different from the literature.

Apparent combined P450C17 and P450C21 deficiency is a rare variant of congenital adrenal hyperplasia. POR deficiency (PORD) is a unique congenital adrenal hyperplasia variant that manifests with glucocorticoid deficiency and DSD, and with/without skeletal malformations. PORD manifests with virilized female genitalia, despite the low levels of circulating androgens in the postnatal period. CAH variant illustrates the existence of an alternative pathway toward the biosynthesis of active androgens in humans that is active in human fetal life only. Severely affected female infants for POR gene are virilized because of defective aromatase activity, and because of the diversion of 17-hydroxyprogesterone to DHT via the “backdoor pathway” to androgens that bypass DHEA, androstenedione, and testosterone. POR is a protein that transfers electrons from NADPH to all microsomal cytochrome P450 enzymes and three steroidogenic enzymes: P450c17 (17α-hydroxylase/17,20lyase), P450c21 (21-hydroxylase), and P450aro (aromatase). Steroids requiring 2 activities impaired by PORD are low. For example, cortisol requires hydroxylations mediated by CYP17A1 and CYP21A2, and cortisol deficiency is essential in these cases. DHEAS and androgens require 2 reactions catalyzed by CYP17A1, and androgens are always low. Steroids proximal to all blocks are high. Progesterone is always elevated in PORD. In our cohort, 2 patients with prenatal virilization (Prader 5) associated with adrenal nodularity and postnatal undervirilization suggested the possibility of POR gene mutation without skeletal phenotype of Antley-Bixler syndrome. These 46,XX patients were born with virilized genitalia, but their basal and ACTH-stimulated circulating adrenal androgens and cortisol levels were low with high levels of 17- hydroxyprogesterone and progesterone. Their virilization did not progress. Interestingly, one of them also had homozygous 21-hydroxylase gene mutation (IVS2-656A/C> G), in spite of absence of postnatal virilization with low levels of adrenal androgens. The possibility of combined 21-OHD and PORD or 17α-hydroxylase/17,20lyase deficiencies is interesting. Scott et al first reported combined POR and 21-hydroxylase deficiencies in a 46,XX newborn with craniosynostosis, salt wasting, minimal virilization, grossly elevated 17-hydroxyprogesterone, and minimally elevated androgen. They found a CYP21B mutation (IVS2-13A/C> G), causing classical 21-hydroxylase

Table 3

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of admission</td>
<td>1.96 ± 2.76 y</td>
</tr>
<tr>
<td>The rate of consangunuity of patients</td>
<td>34/76 (45%)</td>
</tr>
<tr>
<td>Prader score (median)</td>
<td>4</td>
</tr>
<tr>
<td>Salt wasting (n [%])</td>
<td>23/76 (30%)</td>
</tr>
<tr>
<td>Basal ACTH</td>
<td>378.8 ± 664 pg/ml</td>
</tr>
<tr>
<td>Basal 17OH P</td>
<td>90.03 ± 141 ng/ml</td>
</tr>
<tr>
<td>Basal testosterone</td>
<td>673.9 ± 1074 ng/ml</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission</td>
<td>2.5 y</td>
<td>Newborn</td>
</tr>
<tr>
<td>Karyotype</td>
<td>46,XX</td>
<td>46,XX</td>
</tr>
<tr>
<td>Prenatal virilization</td>
<td>Yes (Prader 5)</td>
<td>Yes (Prader 4)</td>
</tr>
<tr>
<td>Postnatal virilization</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Gonads</td>
<td>Bilateral Cystic Ovary</td>
<td>Bilateral Ovary</td>
</tr>
<tr>
<td>Mullerian structures</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Adrenal nodularity</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Basal 17-OH progesterone (ng/ml)</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>ACTH Stimulated Cortisol (g/dl)</td>
<td>3.8</td>
<td>4</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>147-2000</td>
<td>169.9-500</td>
</tr>
<tr>
<td>Adrenal androgens</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Increasing growth velocity</td>
<td>None</td>
<td>None (at age 2 y)</td>
</tr>
<tr>
<td>21-Hydroxylase gen mutation</td>
<td>Homozygous (IVS2-656A/C&gt; G)</td>
<td></td>
</tr>
<tr>
<td>Maternal virilization at pregnancy</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
deficiency, and a POR mutation, A287P, only on the maternal allele, but her clinical characteristics were indistinguishable from patients with mutations on both alleles.\textsuperscript{20} Unfortunately, genetic studies for 17-hydroxylase and POR gene in our patients were terminated, but their clinical and hormonal profile impressively suggested this association. On the other hand, 17,20-lyase deficiency may be due to the inactivating CYB5A mutations.\textsuperscript{21} Idkowiak et al\textsuperscript{21} also reported the concomitant mutations in the P450 oxidoreductase and androgen receptor genes presenting with 46,XY disorder of sex development and androgenization at adrenarche. They considered that both mutant AR and POR were likely to contribute to the neonatal presentation with 46,XY DSD. Virilization at the time of adrenarche appears to suggest an age-dependent, diminishing disruptive effect of both mutant proteins.\textsuperscript{22}

Rarer causes of fetal androgen excess in XX infants are maternal androgen ingestion, maternal virilization disease, fetoplacental aromatase deficiency, sulfotransferase deficiency, virilizing luteoma of pregnancy, and glucocorticoid receptor mutations.\textsuperscript{11,23} In our cohort, 1 patient, aged 13 years, was suggested to have fetoplacental aromatase deficiency from patients with mutations on both alleles.\textsuperscript{20} Unfortunately we could not make any molecular genetic studies for 17-hydroxylase and POR gene in our patients were terminated, but their clinical and hormonal profile impressively suggested this association. On the other hand, 17,20-lyase deficiency may be due to the inactivating CYB5A mutations.\textsuperscript{21} Idkowiak et al\textsuperscript{21} also reported the concomitant mutations in the P450 oxidoreductase and androgen receptor genes presenting with 46,XY disorder of sex development and androgenization at adrenarche. They considered that both mutant AR and POR were likely to contribute to the neonatal presentation with 46,XY DSD. Virilization at the time of adrenarche appears to suggest an age-dependent, diminishing disruptive effect of both mutant proteins.\textsuperscript{22}

Ovarian development disorders are reported second most frequent problem among the patients with 46,XX DSD.\textsuperscript{6,12} In our 46,XX DSD group, interestingly, 1 patient with gonadal dysgenesis (bilateral streak gonad) had virilization at birth, 4 patients had CGD, and 1 had SRY negative ovotesticular DSD. Pubertal delay was the main symptom of this group.

There have been considerable advances in understanding of the early and later stages of ovarian development; a number of genes have been implicated and their mutations have been associated with developmental abnormalities. SRY positivity; WNT4, RPSO1, Catenin gene defects; duplication of SOX9 gene leads to testis-like formation within the ovary (streak gonad, dysgenetic testis or ovotestis) in 46,XX patients. Mutations in FOXL2 are responsible for BPE and can be associated with premature ovarian failure. Ovarian dysgenesis associated with sensorineural deafness is diagnosed as Perrault Syndrome.\textsuperscript{27-29} Two sisters who had 46,XX complete gonadal dysgenesis were diagnosed with Perrault syndrome with ovarian failure due to streak gonads and associated with sensorineural deafness, without BPE. Unfortunately we could not make any molecular genetic analysis in those patients. In a patient who had streak ovaries but virilization at birth, there might be a mutation of one of the ovarian transcription factors.

One patient had 46,XX ovotesticular DSD which are distinct from XX testicular DSD. 46,XX testicular DSD characteristics include male habitus, small testes, and azoospermia with no evidence of uterus or ovaries.\textsuperscript{30} There was no patient diagnosed with 46,XX testicular DSD in our series.

Caudal dysgenesis syndrome (persistent cloacal anomaly) is associated with complex urogenital malformations. Three newborns were diagnosed with cloacal anomaly within the 46,XX DSD group. Persistent cloaca is 1 of the most severe types of anorectal malformations. Appropriate initial drainage is difficult due to their various malformations and hydrocolpos or dilated urinary bladder. One of these patients had urinary hydrocolpos, persistent cloacal canal (common channel > 3 cm), pre-axial polydactyly, horse-shoe multicystic dysplastic kidney, renal diabetes insipidus, and pulmonary stenosis. There was no sign of virilization. Urinary hydrocolpos, cloacal malformation, and pre-axial polydactyly are rare variants of neonatal hydrocolpos. Cloacal dysgenesis with hydrometrocolpos, polydactyly, and congenital heart defect is known as McKusick-Kaufman syndrome (MKKS).\textsuperscript{31,32} MKKS predicted protein shows amino acid similarity to the chaperonin family of proteins, suggesting a role for protein processing in limb, cardiac, and reproductive system development.\textsuperscript{33} Renal problems were present in 90% of cases. Dysplastic kidney reduces the ability to concentrate urine.\textsuperscript{31} A second patient in this group with

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**Table 5**

<table>
<thead>
<tr>
<th>Gender Assignment Recommendation</th>
<th>All Patients with 46,XX DSD</th>
<th>Gender Assignment Recommendation</th>
<th>Female/Male Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gender Assignment</td>
<td>N: 87 (92%)</td>
<td>Accepted</td>
</tr>
<tr>
<td></td>
<td>Recommended</td>
<td></td>
<td>Accepted</td>
</tr>
<tr>
<td></td>
<td>M to F</td>
<td>n = 95</td>
<td>M to F</td>
</tr>
<tr>
<td></td>
<td>F to F</td>
<td>n = 44 (46%)</td>
<td></td>
</tr>
</tbody>
</table>

* The first sex assignment is the parents had made prior to the evaluation by the endocrine team. Second sex assignment is offered by endocrine team after evaluation of patient.
cloacal anomaly presented with Prader 3 genital virilization, uterus bicornatus, and multicystic dysplastic kidney. A third patient with cloacal anomaly had Prader 2 virilization, anal atresia, dilatation of renal ductal system, and patent ductus arteriosus. Children with anorectal and cloacal malformations have a high incidence of association of a syndrome such as VACTERL (vertabral, cardiac, tracheoesophageal, renal, limb) or caudal regression syndrome anomalies include urinary tract, genitalia, and vertebral anomalies including sacrum, cardiovascular, respiratory, and gastrointestinal anomalies. RMKHS was diagnosed in 4 cases with primary amenorrhea. All patients this disease had normal ovarian functions.

Gender rearing of patients with DSD is a big problem. In general, genotypic females with virilizing disorders are raised as females; however, there have been major problems in late-diagnosed patients with severe virilization. “Gender assignment recommendation” could be made in 87 of the 95 patients with 46,XX DSD by the gender assessment team of our university. Parents of 8 patients (8.4%) refused our support for female sex for their children. Eighty-one of 87 patients were raised as females (92%), while 6 patients with late admission and severe degree of virilization were assigned male genders (6%). Gender dysphoria and complaints at pubertal age from raised female sex did not occur in our cases.

Females with classic congenital adrenal hyperplasia are exposed to prenatal and postnatal androgen excess; a high frequency of homosexuality or bisexuality has been observed in these cases. However, it remained controversial which period of androgen exposure is critical for development of these disorders. It is believed that prolonged postnatal androgen exposure is the unique factor associated with male gender identity or homosexual sexual orientation. Only 1 patient in our series, who was raised as female, showed lesbian behaviors at pubertal age. Her external genitalia virilization was at Prader 4 level according to prepubertal phenotypes and poor hormonal control/ high testosterone levels were observed during the growth period in patients with 46,XX DSD.

As conclusion, 46,XX DSD is almost derived from intrauterine virilization and CAH is the most common cause of 46,XX DSD due to fetal androgen exposure. A small group of patients needs extensive evaluation for precise diagnosis. Pubertal delay is the main symptom of patients with 46,XX gonadal gynaecism. Sex assignment recommendation was usually accepted by the family when made at a young age in patients with 46,XX DSD.

The Chicago classification which is based on mainly karyotype of patients, provide more coordinated evaluation of DSD patients. Although 46,XX DSD patients, who are seen less commonly, have heterogeneous characteristics, they can be evaluated under a subgroup of DSD classification. CAH remains the most common cause of ambiguous genitalia, based on the new classification.

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