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Precocious Puberty in a 4-year-old Child with 46,XX Disorder of Sexual Development: A Case Report

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Keyword: 46,XX Disorder of Sex Development; Congenital Adrenal Hyperplasia; Precocious Puberty; Salt-Wasting;

Abstract
Introduction: *Disorders of sex development (DSD) are congenital conditions in which there is a mismatch between chromosomal, gonadal, and phenotypic sex. Among 46,XX patients, the leading underlying disorder is congenital adrenal hyperplasia (CAH) secondary to 21-hydroxylase deficiency. Precocious puberty in 46,XX DSD is rarely documented, particularly in Indonesia.* ***Case description:*** *A four-year-old girl presented with atypical genitalia noted since birth with progressive enlargement resembling clitoromegaly. Physical examination revealed ambiguous genitalia, pubic hair development, and obesity. Laboratory results showed hyponatremia, markedly elevated estradiol, progesterone, and 17-hydroxyprogesterone, with suppressed gonadotropins. MRI demonstrated a uterus, ovary, cervix, vagina with clitoromegaly, and the absence of testicular tissue. Karyotyping confirmed 46,XX with negative SRY gene. Bone age was advanced, corresponding to an 11.5-year-old boy.* ***Discussion:*** *These findings indicated 46,XX DSD due to classical salt-wasting CAH with precocious puberty. In this patient, androgen excess may have induced early puberty through aromatization to estrogen. Pubertal development in DSD can be absent, delayed, incomplete, or prematurely triggered.* ***Conclusion:*** *This case highlights a rare presentation of precocious puberty in a child with 46,XX DSD. It underscores the inherent complexity of DSD, where misalignment between chromosomal, gonadal, and phenotypic sex creates substantial challenges for both diagnosis and clinical management.*

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Introduction

Disorders of Sex Development (DSD) represent a diverse group of congenital conditions in which the formation of internal and external genital structures does not proceed typically. These conditions may arise from genetic variations, disruptions in developmental programming, or hormonal imbalances. In many cases, DSD is recognized at birth because of ambiguous genital appearance, but diagnosis may also occur later, during puberty, or when fertility problems become evident. The frequency of ambiguous genitalia is estimated at approximately 1 in 2,000–4,500 live births (Witchel, 2019); (Welni & Fakhrurrazi, 2023). In Indonesia, epidemiological data remain limited and often underreported. A study that investigated DSD prevalence in the local population highlighted a noteworthy burden, with the prevalence of females carrying XY chromosomes recorded at 6.4 per 100,000 live births and androgen insensitivity at 4.1 per 100,000 live births (Dessens et al., 2015). These findings underscore the clinical variability and significance of conditions that affect sexual differentiation from early fetal life.

This disorder can be categorized according to several levels of sex determination, including genetic, chromosomal, gonadal, hormonal, ductal, and external genital development, as well as secondary sex characteristics, legal sex assignment, and psychological identity. For clinical purposes, however, the classification most often used is that proposed by the Lawson Wilkins Pediatric Endocrine Society and the European Society of Pediatric Endocrinology, which broadly groups cases into: (1) sex chromosome DSD, (2) 46,XX DSD, and (3) 46,XY DSD (García-Acero et al., 2020). Even so, some conditions do not fit neatly into a single category, or may overlap more than one. Beyond the biological aspects, DSD can carry significant medical, social, and psychological consequences, including challenges in sex assignment, fertility, and gender identity (Hughes et al., 2007). Among these categories, 46,XX DSD—most commonly caused by congenital adrenal hyperplasia (CAH)—is of particular interest because its hormonal mechanisms directly contribute to varying degrees of genital masculinization

Most 46,XX DSD cases are attributed to congenital adrenal hyperplasia (CAH). Less common forms are linked to genetic mutations that interfere with gonadal development or steroidogenesis. For instance, aromatase deficiency, caused by mutations in the CYP19A1 gene, can result in atypical genitalia in the infant and maternal virilization during pregnancy (Grouthier & Bachelot, 2024). CAH itself is an autosomal recessive disorder, most often due to 21-hydroxylase deficiency (White & Speiser, 2000); (Carvalho et al., 2021). This enzymatic defect blocks cortisol and aldosterone synthesis, shunting precursors toward androgen production, and can also raise estradiol and progesterone levels. In females, androgen excess has particularly profound effects, leading to varying degrees of masculinization of the external genitalia (El-Maouche et al., 2017). In addition to these effects at birth, chronic androgen elevation in CAH may accelerate bone maturation and disrupt the timing of pubertal onset, thereby increasing the risk of early or rapidly progressing puberty.

Because DSD may affect the process of sexual differentiation, the formation of ovaries or testes and the development of both internal and external genitalia can be altered. When gonadal function is impaired, pubertal development is often disrupted. In practice, puberty in these individuals may be absent, delayed, incomplete, or in some cases, unusually early (Nordenström, 2020). In CAH, unstable hormonal regulation—particularly chronic androgen excess—contributes to the possibility of early pubertal changes, adding further complexity to clinical management. Managing a child with

ambiguous genitalia is therefore complex. Decisions regarding sex assignment, parental and patient education, and long-term medical care require careful consideration. Importantly, "sex" should be distinguished from "gender": sex refers to the biological attributes of internal and external genital structures, while gender encompasses identity and social roles, which cannot be reduced to a purely binary model. This distinction becomes essential in CAH cases, where masculinization and altered pubertal development may influence not only biological outcomes but also psychosocial adjustment.

Case Description

A 4-year-old child was brought to the pediatric clinic with complaints of atypical genital appearance, first noticed by the parents at birth. At delivery, the genitalia appeared female with a midline prominence that progressively enlarged over time. The patient had no complaints related to urination and was able to void through a small opening located beneath the genital structure resembling a penis. The child had a history of recurrent hospital admissions due to dehydration and electrolyte imbalance. The skin was noted to be darker compared to peers. Family history revealed that the patient's younger sibling had similar complaints and died due to unstable electrolyte and blood glucose levels, with a clinical diagnosis of congenital adrenal hyperplasia.

The mother was 23 years old at the time of pregnancy and reported no significant health issues. She underwent regular antenatal check-ups, consumed prescribed vitamins, denied the use of herbal medicine, and had no history of systemic illness during pregnancy. The patient was delivered spontaneously at 39 weeks of gestation with immediate crying at birth, birth weight of 3400 g, and length of 48 cm. There was no history of neonatal jaundice or respiratory distress. Growth and developmental milestones were reported as age-appropriate. The infant was exclusively breastfed for one month, followed by formula feeding, and transitioned to a regular household diet since 1.5 years of age.

Figure 1. Clinical photographs of the patient. (A). Full-body view of the 4-year-old patient, showing normal growth parameters with obesity (>+3 SD for weight-for-height). (B). External genital examination reveals ambiguous genitalia with

clitoromegaly resembling a penile structure and the presence of pubic hair, consistent with 46,XX DSD.

On physical examination, the patient appeared mildly ill with a Glasgow Coma Scale score of 15 (E4V5M6). Anthropometric assessment showed a body weight of 32 kg and height of 120 cm, corresponding to >+3 SD for weight-for-height (obesity). Vital signs were within normal limits. General examination of the head, neck, chest, heart, lungs, and abdomen revealed no abnormalities. Genital examination demonstrated ambiguous external genitalia resembling male-type genital structure with clitoromegaly, accompanied by the presence of pubic hair.

From laboratory findings as seen on table 1, complete blood count was within normal range. Serum chemistry revealed hyponatremia (Na: 132 mmol/L), with other electrolytes, glucose, and albumin values within reference limits. Hormonal analysis demonstrated elevated estradiol (30.70 pg/mL), progesterone (189.58 ng/mL), and markedly increased 17-hydroxyprogesterone (76.55 ng/mL), with suppressed LH (<0.1 mIU/mL) and FSH (<0.3 mIU/mL). Testosterone levels were within reference values.

Tabel 1
Laboratory Results

Complete Blood Count	**Results**	**Reference Range**
Hemoglobin	14.4	10.85 - 14.90 g/dl
RBC	5.17	4.74 – 6.32 x 10^6/µl
Hematocrite	41.7	39.90 – 51.10 %
MCV	80.70	71.80 – 92.00 µm³
MCH	27.90	27.8 – 32 pg
MCHC	31.1	30.8 – 35.20 g/dL
RDW	12.3	11.30 - 14.60 %
WBC	7.81	4.79 - 11.34 x 10^3/mm³
Diff. count	2/0/56/32/10	0-4/0-1/51-62/25-33/2-5
PLT	302	216 - 451 x 10^3/mm³
Clinical Chemistry and Electrolyte Serum		
Natrium (Na)	132	136 – 145 mmol/L
Kalium	4.01	3.5 – 5.1 mmol/L
Klorida	101	98 – 107 mmol/L
Kalsium	9.5	8.6 – 10.0 mg/dL
Fosfor	4.3	2.5 – 4.5 mg/dL
Magnesium	2.05	1.6 2.6 mg/dL
Albumin	4.21	3.5 - 5.2 g/dL
Gula Darah Sewaktu	99	<200 mg/dL
Hormone		
Testosteron	1.16	0.12–0.21 ng/mL
Estradiol	30.70	6.0 – 27 pg/mL
Progesteron	189.58	0.2-1.4 ng/mL
17-OHP	76.55	<1.15 ng/mL
LH	< 0.1	Folicular phase: 2.4-12.6 mIU/ml Ovulation: 14.0 -95.6 mIU/mL Luteal phase: 1.0 -11.4 mIU/mL

FSH	< 0.3	Postmenopause : 7.7 - 58.5 Folicular phase: 3.5 -12.5 Ovulation: 4.7 -21.5 Luteal phase: 1.7 - 7.7 Postmenopause: 25.8 - 134

Abdominal MRI showed the presence of a uterus, right ovary, cervix, and vagina with clitoromegaly, while no testicular tissue was identified. Findings were consistent with 46,XX DSD. In addition, lower vaginal atresia with hydrocolpos was observed. Bone survey demonstrated advanced bone age corresponding to an 11.5-year-old boy, with a predicted adult height maturity of 61.0%. Genetic analysis of this patient revealed karyotype analysis confirmed a 46,XX chromosomal pattern, consistent with female genetic sex. SRY gene testing was negative.

1. Discussion

During prenatal development, sexual differentiation is orchestrated by a complex interaction of genes, proteins, and hormones. Phenotypic sex in humans is primarily determined by gonadal development, which itself is directed by the individual's genetic constitution. Sexual development occurs in two stages: sex determination and sex differentiation. In the first stage, specific genes drive the undifferentiated bipotential gonad to become either ovaries or testes. In the second stage, gonadal hormones regulate the development of internal and external genitalia (Kousta et al., 2010). Several genes play pivotal roles during gonadal determination. For example, WT1, DAX1, SF-1, LHX9, PAX2, GATA4, EMX2, and WNT4 help initiate gonadal differentiation by activating testis-specific pathways or suppressing them, which favors ovarian development (García-Acero et al., 2020). Among these, the nuclear receptor steroidogenic factor 1 (NR5A1) is crucial for adrenal and gonadal steroidogenesis. It is normally expressed in the bipotential gonad and later maintained in the testis but repressed in the ovary. Mutations in SF1 can lead to adrenal and gonadal insufficiency in 46,XY individuals, whereas in 46,XX individuals, they may cause adrenal failure but relatively preserved ovarian differentiation (Guerra et al., 2021).

Despite advances, the full spectrum of genes regulating ovarian development is still not well defined. In the absence of SRY, female differentiation proceeds with ovarian germ cells entering meiosis. Without SRY activation, SOX9 fails to reach the critical threshold required for testis formation. Instead, other factors such as RSPO1, WNT4, and FOXL2 promote ovarian differentiation by stabilizing β-catenin (CTNNB1) signaling, which suppresses SOX9. Conversely, gene duplications such as SOX9 or SOX3 in 46,XX individuals can result in testicular DSD, while deletions of SOX9, SF-1, or WT1 may lead to 46,XY gonadal dysgenesis (García-Acero et al., 2020). Disruptions in sex determination or differentiation can therefore lead to DSD, presenting with discordance between chromosomal, gonadal, and phenotypic sex. Such mismatches may manifest as abnormalities in internal genitalia, atypical external genitalia, or variable degrees of virilization (Guerra et al., 2021). Diagnosis is often challenging due to the wide variability in clinical features, late onset of some symptoms, and inconsistencies between laboratory and phenotypic findings.

The predominant cause of 46,XX disorders of sex development is congenital adrenal hyperplasia, with 21-hydroxylase deficiency being the most frequent underlying defect (Speiser et al., 2010). CAH is an autosomal recessive disease characterized by mutations affecting steroidogenic enzymes, resulting in impaired cortisol and aldosterone

synthesis, compensatory ACTH elevation, adrenal hyperplasia, and androgen overproduction (Bulsari & Falhammar, 2017). An estimated 95% of patients with congenital adrenal hyperplasia have 21-hydroxylase deficiency as the underlying defect. Classical CAH occurs in 1:5,000–1:15,000 live births, while non-classical variants occur more frequently in heterozygous carriers (Merke & Bornstein, 2022). The classical form of CAH is divided into two subtypes: salt-wasting and simple virilizing. The salt-wasting variant, which represents the most severe phenotype, accounts for roughly 75% of classical cases and is characterized by near-complete loss of 21-hydroxylase activity (often <2%). Therefore, cortisol and aldosterone production are markedly reduced, leading to electrolyte disturbances such as hyponatremia, hyperkalemia, and hypovolemia that usually become clinically evident during the first month of life. By contrast, simple virilizing CAH retains partial enzyme activity, leading to androgen excess and ambiguous genitalia without salt-wasting crises (Podgórski et al., 2018).

Pubertal development in CAH can be atypical. Normal feminization may fail, as reflected by absent breast development or amenorrhea. In some female patients, precocious puberty manifests with premature pubic hair and accelerated growth, especially if treatment is delayed beyond infancy (Juniarto et al., 2018). In this case, the patient was diagnosed with 46,XX DSD with a negative SRY gene, confirming that the atypical sexual development was not due to SRY translocation but rather to classical salt-wasting CAH. This diagnosis was supported by markedly elevated 17-hydroxyprogesterone, recurrent electrolyte disturbances, and hyponatremia. The elevated estradiol and progesterone levels may be explained by aromatization of testosterone. The presentation of precocious puberty in this patient likely reflects disrupted gonadal function, a common feature in individuals with DSD.

Conclusion

This case highlights a rare presentation of precocious puberty in a child with 46,XX disorder of sex development caused by classical salt-wasting congenital adrenal hyperplasia. Clinical findings of ambiguous genitalia, recurrent electrolyte imbalance, and elevated 17-hydroxyprogesterone, supported by imaging and genetic analysis, confirmed the diagnosis. The case underlines the complexity of DSD, in which discordance between chromosomal, gonadal, and phenotypic sex poses significant diagnostic and management challenges. Early recognition, comprehensive hormonal and imaging evaluation, and confirmation through genetic testing are essential for accurate diagnosis.

Long-term follow-up and multidisciplinary care are required to optimize growth, pubertal development, and psychosocial adjustment. Family education and counseling remain integral to management, ensuring informed decision-making regarding gender assignment and future treatment options.

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