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IUGR ambiguous genitalia in Iran: a case report

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Abstract

Background Pericentric inversion of Chromosome 9 is a common chromosomal abnormality, occasionally linked to clinical conditions such as ambiguous genitalia, warranting its inclusion in differential diagnoses. Sexual ambiguity is a tragic and highly distressing condition that imposes deep emotional and spiritual concerns on the family. Therefore, it is essential to adopt a rational and immediate approach, including clinical, hormonal, genetic, molecular, and radiographic investigations, to determine its cause and guide the therapeutic strategy.

Case presentation A 35-year-old gravida 1 Iranian woman at 37 weeks of pregnancy delivered a 1900-g newborn via cesarean section due to intrauterine growth restriction. The newborn exhibited ambiguous genitalia, including severe hypospadias and a micropenis. Karyotyping revealed a normal chromosomal count with a pericentric inversion of Chromosome 9 (46XY, inv (9) (p12q13)). Hormonal and ultrasound evaluations were normal, and no family history of sexual development disorders was noted.

Conclusion Pericentric inversion of Chromosome 9 can result in ambiguous genitalia, emphasizing the importance of karyotyping in the diagnostic evaluation for proper management and counseling.

Keywords Ambiguous genitalia, Scrotum, Micropenis, Pericentric inversion

Introduction

Ambiguous genitalia is a condition caused by a disorder of sexual development, leading to congenital anomalies in which the external genitalia do not resemble typical male or female characteristics [1]. Disorders of sex development (DSDs) are characterized by atypical development of chromosomal, gonadal, or anatomical sex [2]. The overall incidence of ambiguous genitalia is approximately 1 in 4500 births, although mild forms of male under-virilization or female virilization may occur in around 2% of live births [3, 4]. In most cases, ambiguous genitalia can be identified at birth owing to unclear characteristics of the external genitalia [5]. In genetic females, ambiguous genitalia are commonly caused by conditions such as congenital adrenal hyperplasia (CAH), exposure to substances with androgenic effects during pregnancy, or the presence of a male hormone-producing tumor in the fetus or mother. In genetic males, potential causes include Leydig cell aplasia, 5-alpha-reductase deficiency, androgen insensitivity syndrome, or exposure to substances with estrogenic effects during pregnancy [6]. Ambiguous genitalia in DSD 46 and XY conditions can manifest in varying degrees [7]. Approximately half of underutilized males do not receive a definitive diagnosis. Studies indicate that these infants tend to have lower birth weights than those with an identified underlying cause [8, 9]. In addition, hypospadias have been linked to intrauterine growth restriction (IUGR) [10].

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Case report

On 4 December, in a city in Iran, a 35-year-old rural Iranian woman, gravida 1, at 37 weeks of pregnancy (based on the first day of her last menstrual period) was admitted owing to intrauterine growth restriction (IUGR). After initial preparations and preparing the mother, a cesarean section was performed at 9:45 a.m. The newborn weighed 1900 g, had a length of 32 cm, and had an Apgar score of 9 and 10, along with signs of ambiguous genitalia. The parents of the newborn had no kinship, and no history of specific diseases, medication use, or allergies was reported in the parents, nor was there any history of a newborn with ambiguous genitalia or other sexual development disorders in their family history. The mother had received standard prenatal care. It is noteworthy that during the first-trimester ultrasound, the gender of the fetus was reported as ambiguous genitalia. Therefore, at 15 weeks of pregnancy, the mother underwent amniocentesis to perform a karyotype, which showed the genotype of the fetus with a normal chromosomal count and a pericentric inversion of Chromosome 9, with a karyotype of 46XY, inv (9) (p12q13). The phenotypic abnormality was attributed to the inversion of Chromosome 9 (Fig. 1).

During the physical examination of the newborn by a pediatrician, a scrotum (with a wrinkled appearance) resembling labia, along with severe hypospadias and a micropenis, was observed (Fig. 2). Owing to the IUGR, the newborn was transferred to the neonatal intensive care unit (NICU). The electrolyte and glucose levels of the patient were normal. The testosterone (T) and dihydrotestosterone (DHT) levels, measured 2 days after birth, were normal for the newborn's age. The ultrasound did not show any signs of female genitalia. Further diagnostic tests at 2 months suggested a probable diagnosis.

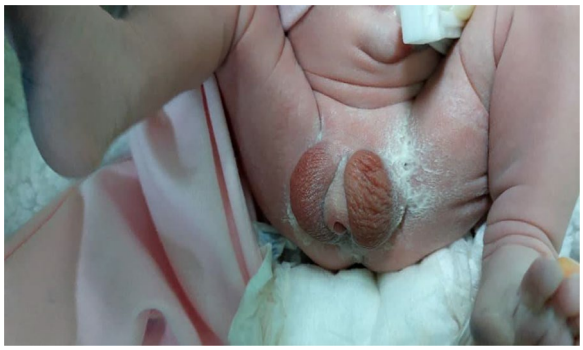

Fig. 2 The appearance of the neonate's genitalia with 46XY, inv (9) (p12q13): scrotum with folds resembling labia, accompanied by micropenis

Discussion

During the development and formation of fetal sex and external genitalia, various factors such as chromosomal structure, gonads, and enzymes play significant roles. During the embryonic period, at the time of zygote formation, a primordial gonad is formed, whose cells possess equal potential to differentiate into testes or ovaries. The first stage of sexual differentiation occurs in the gonads and is influenced by chromosomal structure. In chromosomal structure XY, the primordial gonad develops into testes, whereas in XX conditions, it develops into ovaries. The process of gonadal differentiation into testes is completed by week 8 of gestation. However, if this sequence does not occur, the primordial gonad, without being

Fig. 1 A karyotype of 46XY, inv (9) (p12q13)

influenced by the HY-antigen (HY-AG), will naturally develop into an ovary by week 12 of gestation.

Sexual ambiguity or ambiguous genitalia in humans refers to a condition where there is a mismatch or lack of coordination between the morphology of the gonads and the external genitalia. Sexual ambiguity is classified into two types: true hermaphroditism and pseudohermaphroditism. True hermaphroditism occurs when an individual has both testicular and ovarian tissues. In these patients, the external genitalia exhibit various degrees of intermediate masculinization and feminization. During puberty, the development of masculine and feminine secondary sexual characteristics occurs in different forms. Approximately two thirds of individuals with this condition have a 46, XX karyotype; about one tenth have a 46, XY karyotype; and the remainder exhibit chromosomal mosaicism.

Pseudohermaphroditism is further divided into two types: female and male pseudohermaphroditism. Some male characteristics characterize female pseudohermaphroditism, which can be classified into various categories, each associated with a specific enzyme deficiency and distinct clinical features. The most common form is congenital adrenal hyperplasia, caused by 21-hydroxylase deficiency, which is the leading cause of sexual ambiguity in neonates. Male pseudohermaphroditism occurs when the individual exclusively has testicular tissue, but the external genitalia is feminized or incompletely masculinized [11].

Genital ambiguity is considered the most severe condition within the DSD spectrum and is classified as a medical emergency [7, 12]. It is a rare disorder with a controversial global prevalence [7]. Depending on its cause, DSD can have lifelong impacts, influencing not only sexual differentiation but also pubertal development and fertility in adulthood [12].

This report describes a case of a successful live birth from a couple with no history of any diseases, medication use, or consanguinity in which the newborn boy has ambiguous genitalia and a karyotype with inv (9) (p12q13). Pericentric inversion of Chromosome 9 is a common chromosomal anomaly that should be considered in the differential diagnosis of ambiguous genitalia [11]. Abnormal sexual ambiguity, including hypospadias, micropenis, and cryptorchidism, has been previously reported in cases of pericentric inversion of Chromosome 9 (inv(9)(p12q13) [13–15].

Chromosome 9 inversion (inv(9)) was traditionally regarded as a benign variant with no clinical phenotypic effects [16]. However, recent studies utilizing classical cytogenetics have suggested a potential link between inv(9) and conditions such as infertility [17, 18] and recurrent miscarriages [19]. In addition, research has indicated associations with azoospermia, congenital anomalies, growth retardation, and, in rare cases, abnormal phenotypes [20, 21].

Determining fetal sex is crucial, as it significantly impacts the newborn's future. In cases of gender ambiguity, two key factors are essential: timely sex identification and appropriate treatment decisions [22]. Sex determination is typically based on factors such as the newborn's genotype (chromosomal analysis results) and pelvic sonography. Treatment often involves reconstructive surgery to modify or remove the genitalia in alignment with the assigned sex, along with hormone replacement therapy [23].

Conclusion

Early diagnosis, facilitated by advancements in genetic technologies, plays a critical role in providing appropriate interventions. Genetic counseling is essential to assess the family history, parental consanguinity, and the presence of similar conditions in other siblings, which can help guide clinical decisions and treatment strategies. Timely diagnosis and management are crucial in addressing the needs of patients with ambiguous genitalia and related disorders of sexual development (DSD), allowing for better long-term outcomes and improved quality of life for affected individuals.

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Author contributions
MA contributed to all study aspects, including data collection and manuscript preparation, and was the project coordinator. MSh was actively involved in managing the case and drafting the manuscript. AM participated in the active management of the case. All authors reviewed and approved the final manuscript.

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Availability of data and materials
The data underlying the findings of this study can be accessed within the article.

Declarations

Ethics approval and consent to participate
As this was a case report on a rare disease, ethical approval was waived by the institution.

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors have declared no competing interests.

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