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A Case Report of Phenotypic Discrepancy in Sex Determination and Implications for Genetic Testing and Counseling

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Abstract

This case report presents an extraordinary instance of a 7-month-old male infant with an XX chromosomal pattern—a genetic configuration typically associated with females—while displaying characteristic male physical traits. This anomaly challenges established concepts of sex determination and highlights the intricate interplay between genetic factors and phenotypic expression. The aim of this report is to delve into the clinical implications of this rare presentation and to explore its broader significance for understanding human sex development. The infant's mother, a 20-year-old primigravid Caucasian woman with a medical history of type 2 diabetes managed with Metformin and significant maternal obesity (BMI = 37), underwent a comprehensive prenatal evaluation, including Natera DNA testing. Initial genetic testing revealed an XX chromosomal pattern with a low risk for chromosomal abnormalities. However, subsequent ultrasounds revealed male genitalia, leading to further investigations for congenital adrenal hyperplasia (CAH). Despite normal hormone levels and negative genetic screens for CAH, the newborn exhibited male physical characteristics at birth. This case underscores a significant discrepancy between genetic predictions and observed phenotype, highlighting the limitations inherent in current prenatal genetic testing technologies and the complexity of sex determination mechanisms. The discrepancy observed in this case underscores the critical need for a nuanced approach to genetic evaluation and counseling. It illustrates the limitations of relying solely on genetic tests to predict phenotypic outcomes and emphasizes the importance of integrating clinical, genetic, and phenotypic data in diagnostic processes. A multidisciplinary approach involving geneticists, endocrinologists, pediatricians, and genetic counselors is essential for managing such complex cases effectively. This case advocates for further research into the genetic and environmental factors influencing sex development to enhance diagnostic accuracy and refine personalized care strategies. Ultimately, this report aims to contribute to a deeper understanding of sex development anomalies, advocating for improved diagnostic practices and comprehensive patient support in addressing these rare and complex conditions.

Keywords: Sex determination anomalies; Genetic counseling; Prenatal genetic testing; Intersex variations; Multidisciplinary collaboration; Phenotypic discrepancy; Natera DNA testing; Clinical genetics

Abbreviations

SRY - Sex-determining Region Y; SOX9 - SRY-Box Transcription Factor 9; DAX1 - Dosage-Sensitive Sex Reversal, Adrenal Hypoplasia

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Congenita, Critical Region on the X Chromosome, Gene 1; SF1 - Steroidogenic Factor 1; WNT-4 - Wingless-Type MMTV Integration Site Family, Member 4; NIPT - Non-invasive Prenatal Testing; CVS - Chorionic Villus Sampling; AFI - Amniotic Fluid Index; CAH - Congenital Adrenal Hyperplasia; DOL - Day of Life; CMP - Comprehensive Metabolic Panel; FISH - Fluorescence In Situ Hybridization; DHEA – Dehydroepiandrosterone; eGFR - Estimated Glomerular Filtration Rate; BUN - Blood Urea Nitrogen; NB – Newborn; SCID - Severe Combined Immunodeficiency; G2P1001 - Gravida 2, Para 1, Term Births 1, Preterm Births 0, Abortions 0, Living Children 1; BMI - Body Mass Index

Introduction

In this case report, we present a unique scenario involving a 7-month-old boy with XX chromosomes, a genetic makeup typically associated with females, yet exhibiting typical male physical characteristics. This anomaly challenges conventional understandings of sex determination and underscores the complexity of intersex variations. Through this case, we aim to explore the clinical implications and broader implications for understanding sex development.

In humans, sex determination is typically governed by the presence of specific sex chromosomes. Males typically have XY chromosomes, wherein the Y chromosome carries genes responsible for male development, while females usually have XX chromosomes. The SRY gene on the Y chromosome initiates the development of male reproductive structures, including the testes. In contrast, the absence of the Y chromosome leads to the development of female reproductive structures [1].

In human sex development, SRY-Box Transcription Factor 9 (SOX9), - Dosage-Sensitive Sex Reversal, Adrenal Hypoplasia Congenita, Critical Region on the X Chromosome, Gene 1 (DAX1), Steroidogenic Factor 1 (SF1), and Wingless-Type MMTV Integration Site Family, Member 4 (WNT-4) play critical roles in guiding the differentiation of gonads and the development of internal and external genitalia as well. SOX9, activated by the Sex-determining Region Y (SRY) gene on the Y chromosome, is pivotal in initiating testis development by promoting the differentiation of supporting cells into Sertoli cells within the developing gonad. DAX1, encoded by the NR0B1 gene on the X chromosome, acts as a key regulator in ovarian development, suppressing testis determination pathways and ensuring proper ovarian follicle formation. SF1 (Steroidogenic Factor 1), encoded by the NR5A1 gene, plays a dual role in both testicular and ovarian development, regulating steroidogenesis and supporting the development of the gonadal structures. WNT-4, part of the Wnt signaling pathway, promotes ovarian differentiation by antagonizing the testis-promoting effects of SOX9 and fostering the formation of female-specific structures. Together, these genes orchestrate the intricate processes of sex determination and differentiation, ensuring the establishment of male or female phenotypes in humans [2].

Accurate prenatal genetic testing, including innovative technologies like Natera DNA testing, which we also used in this case, holds immense significance in providing expectant parents with valuable insights into the health and development of their unborn child. Natera's advanced genetic screening methods offer an analysis of the fetus's DNA by rapid sequencing of DNA or RNA samples, enabling early detection of chromosomal abnormalities and genetic disorders [3].

By leveraging techniques such as non-invasive prenatal testing (NIPT), Natera DNA testing provides parents with a non-invasive and highly accurate means of assessing fetal health, minimizing risks associated with traditional invasive procedures like amniocentesis or chorionic villus sampling (CVS) [4]. This early detection empowers parents to make informed decisions about their pregnancy journey, facilitating timely medical interventions, and ensuring access to appropriate support and resources. The integration of Natera DNA testing into prenatal care underscores a commitment to proactive healthcare practices, ultimately enhancing the well-being of both parents and their future children.

The anomaly in this case presents a significant contradiction between the genetic prediction from Natera DNA testing, indicating an XX chromosome pattern, and the actual male phenotype observed in the infant. Despite the anticipated genetic profile, the newborn exhibits clear male external and internal physical characteristics. This discrepancy highlights the complexity of sex determination and the limitations of current genetic screening methodologies, necessitating further investigation into the underlying mechanisms. This exceptional case challenges conventional understanding of sex determination and genetic prediction, emphasizing the need for accurate diagnosis, appropriate medical interventions, and psychosocial support. The objective of this case report is to analyze the clinical, genetic, and psychosocial aspects, contributing to better understanding and care for individuals with similar presentations in the future, and advocating for multidisciplinary approaches to patient management.

Case Presentation

Initial Presentation

Maternal Demographics:

Mother was a 20-year-old, white female presenting for prenatal care as a Gravida 2, Para 1, Term Births 1, Preterm Births 0, Abortions 0, Living Children 1 (G2P1001).

Clinical History:

This pregnancy was complicated by type 2 diabetes

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mellitus for which the mother took Metformin, maternal obesity with pre-pregnancy body mass index (BMI) of 37, and anemia of pregnancy. Mother had no personal or family history of genetic abnormalities.

The mother presented for prenatal care starting at 8 weeks, with her gestational age confirmed by a 9-week sonogram. The mother completed NIPT at 8 weeks gestation. Natera Horizon was negative for all genetic diseases screened for and Panorama showed low risk for chromosomal abnormalities, female sex, and 3.8% fetal fraction.

An anatomy ultrasound was done at 23 weeks and showed male sex with no structural abnormalities. Amniotic Fluid Index (AFI) was normal, and the baby's estimated fetal weight was in the 67th percentile. After her anatomy ultrasound, the mother repeated her Natera testing at 28 weeks' gestation which again showed female sex, low risk for chromosomal abnormalities, and a fetal fraction of 14.8%.

Maternal fetal medicine was consulted for concern of congenital adrenal hyperplasia and repeat ultrasound at 30 weeks confirmed male genitalia. The mother was offered amniocentesis, but she declined. At this point, the differential diagnosis was SRY translocation vs. congenital adrenal hyperplasia (CAH) and further testing was delayed until the child was born.

The mother gave birth to a healthy, 9 lb 3 oz male at 39 weeks' gestation. Baby's Apgar's were 5 and 8 at 1 and 5, respectively. On the initial physical exam, the baby had normal external male genitalia, bilaterally descended testes, and was tanner stage 1.

Investigation and Outcomes

At 1 day of life (DOL), urology saw the baby and determined that his external genitalia were normal. Mother desired circumcision, but urology recommended waiting until baby's workup was complete. The baby also received a Comprehensive Metabolic Panel (CMP) and hormonal testing for congenital adrenal hyperplasia. Results are shown below. On DOL 2, the baby had a scrotal and pelvic ultrasound which showed normal testes descended into the scrotum bilaterally and no uterus or ovaries in the pelvis.

On DOL 3, pediatric endocrinology saw the baby and agreed with the working differential diagnosis and expanded it to include an SRY – male. They suggested that if the baby was SRY negative, he could have mutations in SOX-9, DAX1, SF1, or WNT-4 genes.

The baby's genetic screening came back negative for CAH. He also received a Fluorescence In Situ Hybridization (FISH) analysis which showed XX, SRY negative and no abnormalities on chromosomes 13, 18, and 21.

Yet, the baby has been unable to be tested for SOX-9, DAX1, SF1, or WNT-4 genes. Currently, the working diagnosis is a 46 XX SRY negative male. The baby's mother is going to be referred to another medical facility to finish her baby's work up (Table 1-3).

Table 1: Hormonal Panel Results.

Test	Results	Reference Range
Testosterone Total	<10 ng/dL	no reference for this age group
DHEA (Dehydroepiandrosterone)	59 ng/dL	No range established
Androstenedione	44 ng/dL	< or = 290 ng/dL
11-Deoxycortisol (Compound S)	54 ng/dL	< or = 170 ng/dL
17-Hydroxyprogesterone	24 ng/dL	< 460 ng/dL
17-Hydroxypregnenolone	64 ng/dL	< or = 3013 ng/dL
Deoxycorticosterone	<16 ng/dL	No range established
Cortisol	0.6 mcg/dL	< or = 14 mcg/dL
Progesterone Level	12.9 ng/mL	No range established

Table 2: Blood Chemistry Results

Test	Results	Reference Range
Sodium	140 mmol/L	130-145 mmol/L
Potassium	4.9 mmol/L	3.7-5.9 mmol/L
Chloride	102 mmol/L	97-108 mmol/L
Bicarbonate	22 mmol/L	20-30 mmol/L
Anion Gap	16	
Blood Glucose	60 mg/dL	50-90 mg/dL
BUN	4 mg/dL	2-19 mg/dL
Creatinine	0.4 mg/dL	0.3-1 mg/dL
eGFR	56.37	low < 60
Calcium	10.1mg/dL	7.6-10.4 mg/dL

Table 3: Newborn Screening Results

Screening Test	Result
Initial Phenylketonuria Screen	Normal
Amino Acid Disorders Newborn (NB) Screen	Normal
Fatty Acid Disorders NB Screen	Normal
Organic Acid Disorders NB Screen	Normal
Galactosemia NB Screen	Normal
Biotinidase Deficiency NB Screen	Normal
Hypothyroidism NB Screen	Normal
Congenital Adrenal Hyperplasia NB Screen	Normal
Hemoglobinopathies NB Screen	Normal
Cystic Fibrosis NB Screen	Normal
Severe Combined Immunodeficiency (SCID)	Normal
NB Screen Comments	first screen
Adrenoleukodystrophy Newborn Screen	Normal
Spinal Muscular Atrophy NB Screen	Normal

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Discussion

The presented case offers profound clinical implications that underscore the necessity of thorough genetic evaluation and counseling for families encountering similar situations. Firstly, it highlights the complexities surrounding sex determination and the limitations of relying solely on prenatal genetic testing results. Despite advances in genetic screening technologies like Natera DNA testing, cases such as this emphasize the importance of comprehensive genetic assessment, including careful consideration of both genotype and phenotype.

In the current literature there have been reports following discrepancies in phenotype and genotype discrepancies with fetal blood sampling and karyotyping with genetic amniocentesis, chorionic villus sampling. In a specific case, a 32-year-old Caucasian woman in her second pregnancy at 27 weeks' gestation was diagnosed with a complex fetal cardiac malformation. Her husband had two brothers with cardiac malformations. Ultrasound revealed a left hypoplastic ventricle with aortic and mitral atresia, while external genitalia appeared phenotypically female. Genetic testing via amniocentesis showed a karyotype of 46, XY. Following extensive counseling, the parents opted for termination of pregnancy due to the poor prognosis. After medical induction, delivery of a 1000-g fetus with female external genitalia was observed. Postmortem examination revealed the absence of uterus, Fallopian tubes, and vagina, with microscopic examination showing hypo-trophic testicles. The diagnosis of androgen insensitivity syndrome was suspected based on these findings [5].

Another case report involved a term infant delivered without complications. Non-invasive prenatal screening (NIPS) at 11 weeks' gestation indicated a male fetus with no aneuploidy detected. Despite this, mid-gestation ultrasound showed female external genitalia and a single amniotic sac, prompting a repeat NIPS at 22 weeks, which again confirmed a genetic male. Postnatal chromosome analysis of peripheral blood revealed a 46, XX karyotype, suggesting maternal chimerism was considered but maternal karyotyping was declined. The early demise of a male co-twin (vanishing twin syndrome) was deemed the most likely cause of the discrepancy [6]. These cases exhibit similar anomalies to ours but differ in specific details. Notably, our case is distinct as it has not been documented in published literature, highlighting its unique features and contributing to our understanding of rare sex development anomalies.

Moreover, the case underscores the critical role of genetic counseling in providing families with accurate information, emotional support, and guidance throughout the diagnostic and decision-making process. Genetic counselors play a pivotal role in helping families navigate the complexities of sex determination anomalies, facilitating informed choices regarding medical interventions, psychological support, and future family planning. They serve as advocates for patients and families, ensuring that their concerns are addressed, and their needs are met [7].

The importance of multidisciplinary collaboration in managing complex cases of sex determination anomalies must be emphasized. A team approach involving geneticists, endocrinologists, pediatricians, psychologists, and social workers ensures comprehensive evaluation, personalized care planning, and holistic support for affected individuals and their families. This collaborative effort fosters a patient-centered approach, addressing medical needs, psychosocial well-being, and long-term outcomes [8].

The case highlights the urgent need for further research into the genetic and developmental mechanisms of sex determination, aiming to improve the accuracy of prenatal genetic testing. Current technologies have advanced, but cases like this underscore their limitations in predicting phenotypic outcomes solely from genetic data. Longitudinal studies have been proven to be beneficial in tracking the lifelong health implications of individuals with atypical sex development, informing global clinical guidelines, interventions, and standardized protocols for genetic testing and counseling to ensure consistent and comprehensive care worldwide [9].

Ethical concerns in disclosing unexpected genetic findings in cases of sex determination anomalies are critical to uphold patient autonomy, promote beneficence, and prevent harm. Patients and families may experience profound emotional impact upon learning that a child's genetic sex differs from their observed phenotype, leading to shock, confusion, anxiety, and distress. Healthcare providers must approach disclosure with sensitivity, empathy, and cultural competence, ensuring adequate support and resources are available. Additionally, it has been proven that individuals with atypical sex development may face stigma and discrimination due to societal biases [10]. Proactive measures such as education, advocacy, and referrals to support groups are essential to mitigate potential harm.

Conclusion

This case report underscores the challenges posed by atypical sex determination and the limitations of current genetic testing methods. The presented case of a 7-month-old boy with an XX chromosomal pattern, typically associated with females, yet exhibiting male external genitalia, highlights the complexity of human sexual development. Despite advances in prenatal genetic screening, such as Natera DNA testing, which initially predicted an XX genotype, the observed male phenotype raises significant clinical and ethical considerations. This anomaly prompts critical reflection on the necessity for comprehensive genetic evaluation and

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multidisciplinary care in managing discrepancies between genotype and phenotype.

Genetic counseling emerges as pivotal in providing families with informed decision-making support amidst complex diagnostic uncertainties. Multidisciplinary collaboration among geneticists, endocrinologists, pediatricians, psychologists, and social workers is essential to ensure holistic care and optimal outcomes for affected individuals. Further research into the genetic and developmental mechanisms of sex determination is crucial to enhance diagnostic accuracy and improve patient care standards. By addressing these challenges, we strive to advance our understanding, support affected families and promote equitable healthcare practices in the field of differences of sex development.

Consent To Publish

All authors have contributed to, read, and approved/ consented to publish the final version of manuscript for submission and publication in the journal. We confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal. The authors also declare that they have no competing interests. I thank you in advance for consideration of this brief report for publication in the journal.

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