Case Report: Coexistence of Jacob Syndrome, congenital Adrenal Hyperplasia, and Ambiguous Genitalia in a Male Infant

Qaisar Ali Khan[1], Faiza Hadi[2], Amritpal Kooner[3], Amber Lee[4], Rahma Ahmed[5], Adithya Nadella[6], Harshawardhan Pande[7], Yaxel Levin-Carrion[8], Muhammad Afzal[9], and Moses Alfaro[10]

[1]Khyber Teaching Hospital, MTI KTH, Peshawar
[2]Mercer University School of Medicine
[3]Midwestern University Chicago College of Osteopathic Medicine
[4]Arkansas College of Osteopathic Medicine
[5]Kennesaw State University
[6]Nanjing Medical University
[7]St Louis University Department of Molecular Microbiology and Immunology
[8]Rutgers New Jersey Medical School
[9]St George's University True Blue Campus
[10]The University of Texas Health Science Center at San Antonio Joe R and Teresa Lozano Long School of Medicine

June 12, 2023

Title Page

Submission Category: Case Report

Title: Case Report: Coexistence of Jacob Syndrome, congenital Adrenal Hyperplasia, and Ambiguous Genitalia in a Male Infant.

Qaisar Ali Khan[1]; Faiza Amatul-Hadi, BS[2]; Amritpal Kooner, MA[3]; Amber Lee[4], Rahma Ahmed[5,] Adithya Nadella[6] Harshawardhan Pande [7] , Yaxel Levin- Carrion [8],Muhammad Afzal[9],

Moses Alfaro, BSA[10]

Affiliations:

1. Khyber Teaching Hospital MTI KTH, Peshawar, Pakistan
2. Mercer University School of Medicine, Macon, GA, USA
3. Chicago College of Osteopathic Medicine, Downers Grove, IL, USA
4. Arkansas College of Osteopathic Medicine, Fort Smith, AR, USA
5. Kennesaw State University, Kennesaw, GA, USA
6. Nanjing Medical University, Nanjing, China
7. Saint Louis University, Missouri, USA
8. Rutgers New Jersy Medical School, New Jersy, USA
9. St. George's University School of Medicine, True Blue, Grenada
10. Long School of Medicine at the University of Texas Health Science Center San Antonio, San Antonio, TX, US

Corresponding author: Muhammad Afzal

St. George's University School of Medicine, True Blue, Grenada

mafzal@sgu.edu

Manuscript Word Count: 2775

Number of Figures: 2

Number of Tables: 1

Statement and Declarations

The authors report no conflicts of interest.

No funding sources were utilized in the composition of this research.

Consent: A written informed consent was taken from the infant's parents to publish this case or any accompanying images.

Abstract: A 5-month-old male infant was evaluated for ambiguous genitalia. Examination revealed cryptorchidism, inguinal hernia, long phallus, and grade 3 scrotal hypospadias. Serum 17- OH progesterone was high and chromosomal analysis showed 47XYY/45XO. A diagnosis of Jacob and CAH was made. The parents were counseled about the patient's condition. He was given hydrocortisone and referred to the pediatric surgeon for further management.

Key clinical message: Jacob syndrome and congenital adrenal hyperplasia are separate entities but share common clinical features such as ambiguous genitalia. Further studies are needed to conclude the relationship between Jacob syndrome and congenital adrenal hyperplasia.

Keywords: congenital adrenal hyperplasia, Jacobs syndrome, XY karyotype, virilization

Introduction

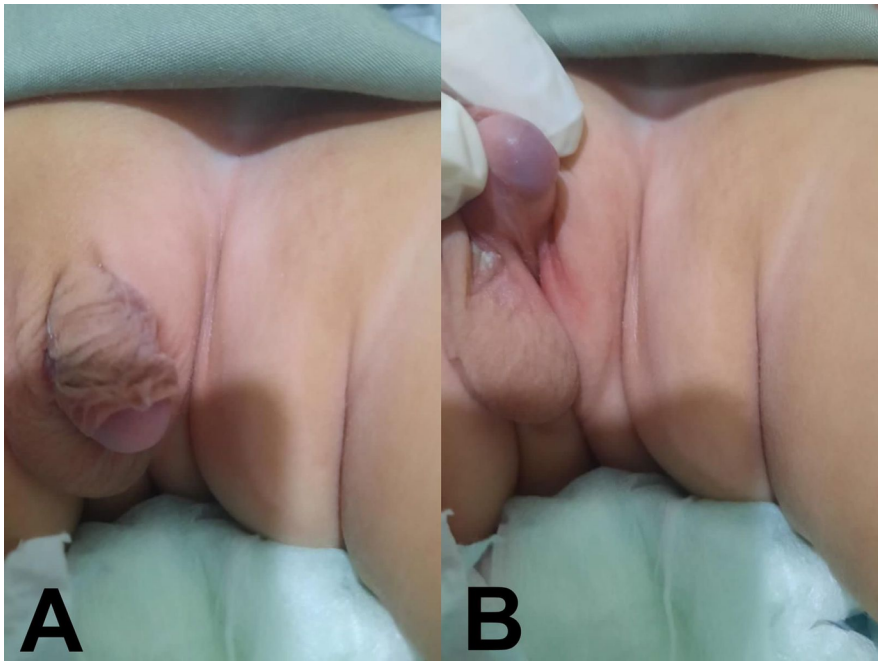
Congenital adrenal hyperplasia (CAH) describes a family of autosomal recessive diseases caused by gene mutations encoding enzymes in the cortisol biosynthesis pathway. The clinical and biochemical manifestations of CAH are quite variable. The most common form of CAH, making up more than 95% of congenital adrenal hyperplasia cases, results from 21-hydroxylase deficiency (21OHD), due to loss of function mutation in CYP21A2. Classic CAH from 21OHD occurs in 1:10,000 to 1:20,000 live births with a female/male ratio of 2:1. **[1]**Disease severity and phenotypic presentation vary depending on the location and extent of gene mutations or deletions, which lead to complex allelic variations.

Jacobs syndrome also known as 47, XYY syndrome, is caused by the insertion of a male Y chromosome to 46, XY. It occurs in 0.1 % of the male population. Additionally, there are no specific clinical manifestations in most boys with the XYY karyotype. Diagnosis of an XYY karyotype is delayed (mean age at diagnosis is 17.1 years) and only 15% of patients are diagnosed with XYY syndrome. The karyotype 47, XYY is relatively common, but its phenotypes are not well-understood. Patients may vary greatly, ranging from no phenotype and relatively few abnormalities to multi-systemic symptoms; for a specific symptom, the severity can vary among individuals. **[2]**

XYY has also been sporadically reported in connection with several cases of disorder of sex development (DSD). Ambiguous genitalia is the condition commonly found in disorders of sex development (DSDs) characterized by imperfect differentiation of external genitalia between males and females. Sex Chromosome mosaicisms like 45 X0/46, XY, or 45 X/47 XYY have been considered major causes of ambiguous genitalia. Such DSD phenotypes of XYY patients include micropenis, testicular dysplasia, true-hermaphrodite, and complete sex reversal.**[3]** Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is a common cause of ambiguous genitalia in genotypically normal female infants (46XX). Most males have no signs of CAH at birth. However, some may present with hyperpigmentation and penile enlargement while those with

salt-wasting disease present early with hyponatremia and hypovolemia. Males with non-salt-wasting disease present later with signs of virilization. In rare forms, males are under-masculinized.[**4**] This report highlights the rare case of congenital adrenal hyperplasia coexisting with Jacobs syndrome presenting as ambiguous genitalia.

Case presentation: A 5-month-old infant was brought to the outpatient department of a tertiary care hospital for ambiguous genitalia. The infant was born at 36 weeks of gestation to a 26-year-old primigravida mother. The marriage was non-consanguineous and the paternal and maternal ages were 30 and 26 years respectively. The pregnancy was complicated due to delayed fertility for three years and the mother revealed the use of herbal medicines during this period. The infant had a birth weight of 3kg with an APGAR score of 9 at both 1 and 5 minutes.



The infant had a height of 90 percentile, a weight of the 50 percentile on the CDC chart, and attained age-appropriate milestones. On examination of the genitalia, there was cryptorchidism with a long phallus and grade 3 scrotal hypospadias as shown in Figure.1. The rest of the clinical examination was unremarkable.

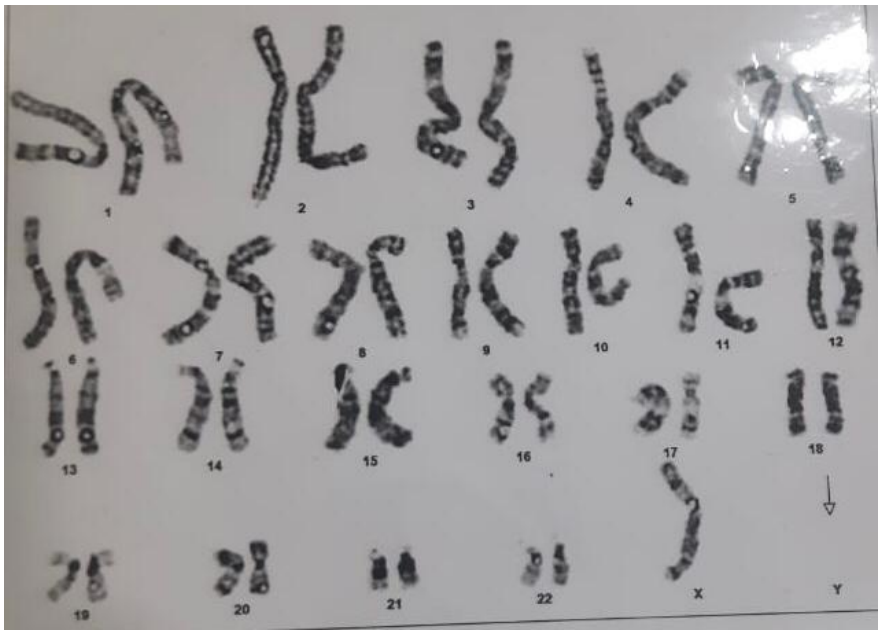
Figure.1: Image presenting long phallus, inguinal swelling (A) left-sided empty scrotum, and hypospadias (B).

Ultrasound of the abdomen and pelvis was ordered that showed bilateral undescended testis with left-sided inguinal hernia. Laboratory investigations including hormonal levels were requested that revealed increased serum 17-OH progesterone levels as shown in Table.1.

Table .1: Hormonal Panel

Investigation	Results	Normal range
Serum cortisol (9 am)	2.6 nmol/L	4.4-25
Serum testosterone	4.9 nmol/L	0.3-4.9
17-OH progesterone	28 nmol/L	12-20
Serum sodium	138 mEq/L	135-145
Serum Potassium	3.8 mmol/L	3.5-5.0

Investigation	Results	Normal range
Serum chloride	98 nmol/L	90-110



A diagnosis of congenital adrenal hyperplasia was made and further genetic study was performed to explore the potential genetic abnormalities associated with the observed features. A total of 30 cells were selected for chromosomal analysis and 21 showed 45X0 while the other 9 showed 47XYY in a mosaic manner that confirmed the diagnosis of Jacob syndrome as shown in Figure.2.

Figure 2: Chromosomal analysis showing 47XYY/45XO

The parents were counseled about the condition, its long-term implication, and possible complications. The patient was started on hydrocortisone 10mg/m^2/day in two divided doses for four weeks and pediatric surgical and urological consultation was arranged to address the patient's urogenital defects. Frequent follow-up was suggested to regularly monitor the patient's hormones, growth, and development.

Discussion

Congenital adrenal hyperplasia (CAH) is a group of inherited disorders that are present at birth where the adrenal glands are hyperplastic, most commonly resulting from mutations or deletions of CYP21A. In CAH, the body is missing an enzyme that stimulates the adrenal gland to release cortisol. Disease severity and phenotypic presentation vary depending on the location and extent of gene mutations or deletions, which lead to complex allelic variations. Almost 300 CYP21A2 mutations have been identified, making genotyping these individuals a cumbersome undertaking. CAH can be seen as a continuum from salt wasting to mild forms but is divided into two categories for convenience: classical approximately 67% ("salt-losing," severe, ex-congenital), and nonclassical approximately 33% ("non-salt-losing" or "simple-virilizing," less severe, formerly known as late-onset or cryptic) according to the degree of aldosterone deficiency Patients with classic CAH may present as simple virilizing CAH or salt-wasting CAH and are usually diagnosed in infancy while patients with non-classical CAH may be asymptomatic or present with a milder form of virilization postnatally. **[5]** CYP21, found on chromosome 6p, near the human leukocyte antigen gene cluster, is the gene for adrenal 21-hydroxylase. Specific mutations may be linked to a degree of enzymatic dysfunction and the

clinical manifestation of 21-hydroxylase insufficiency. Minor mutations on both alleles of the 21-hydroxylase gene are found in patients with non-classic forms [**6**] A retrospective cohort study conducted by Gidlöf et al. in Sweden found the CYP21A2 genotype in 81% of the patients, reflecting improved diagnostic usage of genetic studies. [**7**] The infant we are reporting was diagnosed solely based on clinical findings and laboratory values. Due to financial constraints and resource availability, genetic studies could not be conducted in our case.

It is shown that up to 29.3% of CAH patients had adrenal tumors. Abdominal ultrasound is the modality of choice for small-sized pediatric patients due to the lack of ionizing radiation, lower cost than cross-sectional imaging, and extensive availability. [**8**] In our situation, the ultrasound of the infant resulted in the adrenal glands being normal, ruling out the likelihood of an adrenal tumor.

Symptoms of Jacobs syndrome may be quite vague during childhood, and for this reason, most children go undiagnosed. However, Men with Jacobs syndrome who do display symptoms are most likely to exhibit tall stature and macrocephaly. Developmental delays and behavioral issues have been noted, as well as atonia, clinodactyly (medial curvature of a digit, i.e., 5th finger toward the 4th), and hypertelorism. The incidence of asthma and autism spectrum disorder also appears to be increased in these individuals. [**9**] other conditions such as Marfan syndrome and Sotos syndrome should be ruled out, in contrast to Jacobs syndrome, Marfan syndrome often presents with cardiac abnormalities such as aortic root dilatation and mitral valve prolapse. Sotos syndrome, also known as cerebral gigantism, is a rare genetic condition caused by a mutation in the NSD1 gene. Hallmark features include excessive growth during childhood, macrocephaly, learning disabilities, hypotonia, and seizure disorders. [**10**] Our patient had none of them.

Patients with Jacobs syndrome have been found to have an increased incidence of certain diseases. These include asthma, seizure disorders, and tremors. Some 47, XYY patients have been noted to have genitourinary abnormalities such as microphallus, hypoplastic scrotum, cryptorchidism, and hypospadias. These patients are also at an increased risk for learning disabilities, ADHD, autism spectrum disorder, and speech difficulties. [**11**]

The diagnosis of both CAH and Jacobs syndrome can be done prenatally with amniocentesis or chorionic villus sampling, and treatment involves dexamethasone administered at or before 10 weeks of gestation. A study conducted by Carlson et al. found that prenatal diagnosis and therapy of 21-hydroxylase deficiency is safe and effective in lowering or eliminating virilization in the affected female, sparing the newborn female the repercussions of genital ambiguity, sex misassignment, and gender confusion. [**12**] However, in our case, the mother did not undergo routine antenatal visits during the pregnancy leading to the failure of antenatal diagnosis of CAH as well as Jacob syndrome.

There is no treatment for XYY syndrome. The treatment option is generally only supportive, with attention given to the comorbidities of the patient. While medication cannot treat XYY syndrome, some medications can be used to treat conditions related to the syndrome. A person with XYY syndrome can get help with any learning or developmental delays through speech therapy, occupational therapy, or other assistance. Therapy can also help with ADD/ADHD, social interactions, and other behavioral problems. While The treatment for CAH is based on replacing normal glucocorticoid and mineralocorticoid needs, as well as psychological support [**13,14**] The patient is currently receiving hydrocortisone. The parents of the infant were counseled about the need for genital surgery and psychological support.

Conclusion

This rare case highlights the co-existence of CAH and Jacob syndrome (47, XYY Syndrome) that leads to ambiguous genitalia and various urogenital abnormalities and underscores a stepwise diagnostic approach in patients with atypical presentation. A multidisciplinary approach including endocrinology, surgery, and genetics is necessary for the proper management of complexities associated with the condition. Further research is needed to find the association between CAH and Jacob syndrome in patients with ambiguous genitalia.

Acknowledgments

None

Conflict of interest

The authors report no conflict of interest.

Funding

No funding sources were utilized in the composition of the research.

Author's contributions

Qaisar Ali Khan was responsible for data collection and acquisition of data. Amber Lee, Amritpal Kooner, Rahma Ahmed, Yaxel Levin-Carrion, Moses Alfaro , Muhammad Afzal, Adithya Nadella, and Harshawardhan Pande performed the literature review and wrote the manuscript. Qaisar Ali Khan and Faiza Amatul Hadi reviewed and critically revised the manuscript. All authors have approved the final manuscript.

References

Therrell BL. Newborn screening for congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001, 30:15-30. 10.1016/s0889-8529(08)70017-3.

Kim IW, Khadilkar AC, Ko EY, Sabanegh ES Jr. 47,XYY Syndrome and Male Infertility. Rev Urol. 2013;15(4):188-96. PMID: 24659916; PMCID: PMC3922324.

Yang Y, Chen F, Luo Z,et al. Disorder of Sexual Development Males With XYY in Blood Have Exactly X/XY/XYY Mosaicism in Gonad Tissues. Front. Genet. 2021, 12: . 10.3389/fgene.2021.616693.

Momodu II, Lee B, Singh G. Congenital Adrenal Hyperplasia. [Updated 2023 Jan 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK448098/

Al-Agha AE, Ocheltree AH, Al-Tamimi MD: Association between genotype, clinical presentation, and severity of congenital adrenal hyperplasia: a review. Turk J Pediatr. 2012, 54:323-32.

Pang SY, Wallace MA, Hofman L, et al.: Suwa, Worldwide experience in newborn screening for classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics. 1988, 81:866-74. 10.1016/s0022-5347(17)42164-1.

Gidlöf S, Falhammar H, Thilén A, et al.: One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study. Lancet Diabetes Endocrinol. 2013, 1:35-42. 10.1016/S2213-8587(13)70007-X.

Morani AC, Jensen CT, Habra MA, et al.: Adrenocortical hyperplasia: a review of clinical presentation and imaging. Abdom Radiol (NY). 2020, 45:917-27. 10.1007/s00261-019-02048-6.

New MI, Carlson AD, Obeid JS: Extensive personal experience: prenatal treatment and diagnosis of congenital adrenal hyperplasia owing to steroid 21-hydroxylase deficiency. J Clin Endocrinol Metab. 1995, 80:2014. 10.1210/jcem.80.7.7608248.

Sood B, Clemente Fuentes RW. Jacobs Syndrome. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan

Bardsley MZ, Kowal K, Levy C, Gosek A, Ayari N, Tartaglia N, Lahlou N, Winder B, Grimes S, Ross JL. 47,XYY syndrome: clinical phenotype and timing of ascertainment. J Pediatr. 2013 Oct;163(4):1085-94. doi: 10.1016/j.jpeds.2013.05.037

Forest MG, Bétuel H, David M: Prenatal treatment in congenital adrenal hyperplasia due to 21-hydroxylase deficiency: up-date 88 of the French multicentric study. Endocr Res. 1989, 15:277-301. 10.1080/07435808909039101.

Kim IW, Khadilkar AC, Ko EY, Sabanegh ES Jr. 47, XYY Syndrome and Male Infertility. Rev Urol. 2013;15(4):188-96. PMID: 24659916; PMCID: PMC3922324.

Twayana R, Sunuwar N, Deo S, et al. (August 09, 2022) Salt-Wasting Form of Congenital Adrenal Hyperplasia: A Case Report. Cureus 14(8): e27807. doi:10.7759/cureus.27807.