Virilizing congenital adrenal hyperplasia attributable to steroid 21-hydroxylase deficiency: Case report.

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Abstract

Introduction: Congenital adrenal hyperplasia is a hereditary disorder caused by the failure of adrenal steroidogenesis. 21-Hydroxylase (21OHD) deficiency accounts for 95% of cases. In severe cases, glucocorticoid and mineralocorticoid synthesis is blocked, which may manifest in the neonatal period, childhood, or adulthood.

Clinical case: We present a case of ambiguous genitalia with a 2 cm long phallus or clitoris, scrotal labia majora, and a single genital orifice at the level of the midraphe. The gonads are not palpable.

Diagnostic workshop: The 17OHP level on day 3 of life was 95 ng/mL, and the karyotype was 46,XX. Blood gas analysis at admission revealed metabolic acidosis.

Progress: The patient is being monitored as an outpatient with urinary and serum sodium measurements. No abnormalities have been reported thus far.

Conclusions: Neonatal diagnosis is essential to identify the origin of a hereditary disorder that affects the development of girls' external genitalia and can cause death in infancy due to salt loss. Newborn screening is essential, as is preconception genetic counseling.

Keywords:

Adrenal hyperplasia, sex ambiguity, pseudohermaphrodite, case report.

Abbreviations

ACTH: Adenocorticotropic hormone.
HSC: congenital adrenal hyperplasia.

Additional information

No supplementary materials are declared.

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Not applicable.

Authors' contributions

Ramón Miguel Calixto Vargas Vera: Conceptualization, research, writing—original draft, resources, software, supervision.

Martha Verónica Placencia-Ibadango: Conceptualization, research, writing – original draft, resources, software, supervision.

Cesar William Luciano Salazar: Methodology, Data curation, Formal analysis, Funding acquisition, Project administration, Validation, Visualization, Writing – review and editing.

Kalid Vargas-Silva: Conceptualization, research, writing – original draft.

Sandra Lara-Maruri: Conceptualization, research, writing – original draft.

All the authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic disorder involving the failure of adrenal steroidogenesis due to mutations in the gene encoding the steroid enzyme 21-hydroxylase [1]. The decreased synthesis of hormones such as cortisol and aldosterone causes an increase in upstream products such as 17OHP, without affecting the androgen metabolic pathway. Hyperplasia of the gland occurs due to the compensatory increase in adrenocorticotropic hormone (ACTH) caused by cortisol deficiency. There are three clinical forms of presentation. 1. The classic form involves salt wasting, with 1% enzyme activity. 2. The classic virilizing form without salt wasting, with 2% enzyme activity, and 3. The late form has sufficient enzyme activity for synthesizing mineralocorticoids and cortisol of up to 50%. Signs of late-onset hyperandrogenism are often observed in the follow-up of these patients.

The classic form is the most severe and can be detected in newborn screening programs, and salt loss occurs in 75% of cases [2]. Appropriate genetic counseling is necessary because the frequency of severe mutation carriers in the general population is 1:60, with a frequency of classic neonatal forms of 1:10,000 [3, 4], which is more prevalent in Eskimos. The excess adrenal secretion of androgens that occurs in 25% of cases does not affect the differentiation of external genitalia in males. Hyperandrogenism causes virilization of the external genitalia in girls, resulting in ambiguous genitalia. Congenital adrenal hyperplasia can cause serious problems in the growth and development of children, putting their lives at risk. "Non-classical" congenital adrenal hyperplasia can be partial or late, a milder form of this condition [5]. The cryptic form of the disease may not manifest symptoms in some patients, both men and women. Carriers are healthy patients with a single-allele mutation who do not require specific treatment [6]. The objective of this study is to present the case of a newborn with ambiguous genitalia in a hospital in Guayaquil.

Clinical case

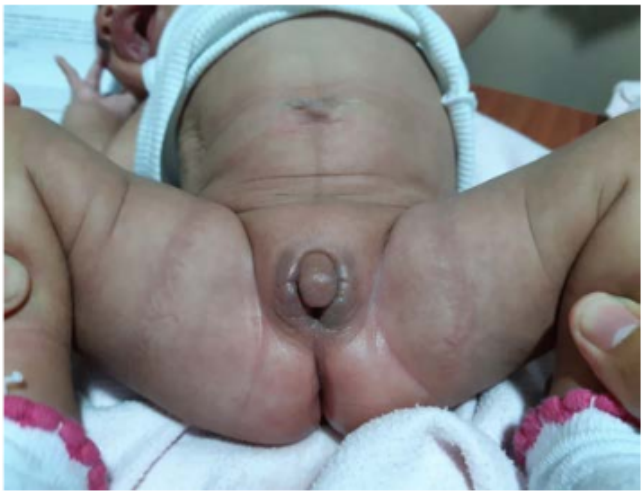
Medical records

This patient is a 21-hour-old newborn, daughter of healthy nonconsanguineous parents, each 25 years old. The newborn is a healthy 7-year-old sister. She was born by simple eutocic delivery with an adequate weight for gestational age, with an APGAR score of 8 at 1 minute. There was no relevant family history. Physical examination revealed ambiguous external genitalia, with a peniform phallus or clitoris 2 cm long, scrotal labia majora, absent testes, and a single genital orifice at the level of the midraphe. Ortolani's sign was negative with symmetrical extremities (Figure 1).

Diagnostic workshop

Both adrenal glands were enlarged; marked thickening of the right posterolateral bladder wall was observed, with increased vascular flow on Doppler imaging. Abdominal and pelvic ultrasound revealed a well-distended gallbladder with wall thickening associated with gallbladder hydrops and no abnormal contents within the gallbladder; the pancreas had no focal lesions, and the kidneys were normal. Transfontanellar ultrasound revealed no abnormalities. At the pelvic level, a uterus with a cervix and a cervical-vaginal cul-de-sac was observed. Colon barium enema revealed no abnormalities. Cystography revealed thickening of the bladder wall toward the right posterior region. Blood gases at admission revealed metabolic acidosis. Cytogenetic analysis of peripheral blood in lymphocyte culture and GTG banding revealed a 46,XX karyotype, corresponding to a normal female karyotype, after 20 metaphases were analyzed without any numerical or structural abnormalities. The 17-hydroxyprogesterone level on the third day of life was 95 ng/mL (reference value: 400- 600 ng/dL).

Figure 1. Physical examination.



Clitoral hypertrophy and fusion of the labia minora (Prader Stage II).

Treatment

The treatment was discharge and follow-up in an outpatient clinic.

Evolution

Serum and urinary sodium levels are kept under control and monitored.

Discussion

The incidence of CAH due to 21-OHD deficiency in Ecuador is unknown, but worldwide, it varies from 1/13,000 to 1/16,000 live births. In 2014, Ocampo et al. [7] reported 11.7 cases per 10,000 positive newborns in the screening test from March to November. This differs from the multicenter evaluation of 13 countries that reported 1 case per 15,000 newborns [8]. In two national hospitals in Mexico, 4 cases are reported yearly, of which 56% and 90% present the classic form of the disease [9, 10]. The Yupik Eskimos of Alaska rank first worldwide, with a rate of 1 case per 280 births, followed by a rate of 1:1367 live births in the population. This incidence varies by race and geographic region. Seventy-five percent of cases of 21(OH)21 deficiency are due to mutations transferred to the CYP21A2 gene by the inactive pseudogene CYP21A1P (CYP21A, CYP21P). Deletions in inactive gene segments cause the remaining 20% of mutations during meiotic recombination [11, 12]. Clitoral hypertrophy, fusion of the labia majora, and the urogenital sinus are observed in the virilizing form of the clinical spectrum. The reproductive organs are normal. Males, at birth, present only scrotal hyperpigmentation and, in some cases, penile growth without showing clear signs of CAH. In the first and second weeks of life, the newborn may present with an adrenal crisis due to the nonvirilizing form of the disease, which is characterized by nausea, vomiting, hyporexia, and lethargy [13]. Importantly, the parents are genetically different, without consanguinity. The newborn presents complete virilization, confirmed by medical examinations and genetic studies, which indicates that the related gene could be more frequent in the Ecuadorian population than currently reported; case series and cross-sectional follow-ups should clarify this question in the future [14].

Conclusions

CAH affects the development of girls' external genitalia and can cause death in infancy due to salt loss. It is a hereditary condition, so preconception counseling, prenatal diagnosis for carriers, and newborn screening are essential for timely treatment.

References

1. Auer MK, Nordenström A, Lajic S, Reisch N. Congenital adrenal hyperplasia. Lancet. 2023 Jan 21;401(10372):227-244. doi: 10.1016/S0140-6736(22)01330-7. Epub 2022 Dec 8. PMID: 36502822.

2. Witchel SF. Congenital Adrenal Hyperplasia. J Pediatr Adolesc Gynecol. 2017 Oct;30(5):520-534. doi: 10.1016/j.jpag.2017.04.001. Epub 2017 Apr 24. PMID: 28450075; PMCID: PMC5624825.

3. Li Z, Huang L, Du C, Zhang C, Zhang M, Liang Y, Luo X. Analysis of the Screening Results for Congenital Adrenal Hyperplasia Involving 7.85 Million Newborns in China: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2021 Apr 23;12:624507. doi: 10.3389/fendo.2021.624507. PMID: 33967952; PMCID: PMC8104032.

4. Huidobro Fernández B, Echeverria Fernández M, Dulin Iñiguez E, Ezquieta Zubicaray B, Roldán Martín MB, Rodríguez Arnao MD, Rodríguez Sánchez A. Neonatal screening for congenital adrenal hyperplasia: transitory elevation of 17-hydroxyprogesterone. J Pediatr Endocrinol Metab. 2011;24(3-4):155-62. PMID: 21648283.

5. Auchus RJ, Witchel SF, Leight KR, Aisenberg J, Azziz R, Bachega TA, Baker LA, Baratz AB, Baskin LS, Berenbaum SA, Breault DT, Cerame BI, Conway GS, Eugster EA, Fracassa S, Gearhart JP, Geffner ME, Harris KB, Hurwitz RS, Katz AL, Kalro BN, Lee PA, Alger Lin G, Loechner KJ, Marshall I, Merke DP, Migeon CJ, Miller WL, Nenadovich TL, Oberfield SE, Pass KA, Poppas DP, Lloyd-Puryear MA, Quigley CA, Riepe FG, Rink RC, Rivkees SA, Sandberg DE, Schaeffer TL,

Schlussel RN, Schneck FX, Seely EW, Snyder D, Speiser PW, Therrell BL, Vanryzin C, Vogiatzi MG, Wajnrajch MP, White PC, Zuckerman AE. Guidelines for Developing Comprehensive Care Centers for Congenital Adrenal Hyperplasia: Guidance from the CARES Foundation Initiative. Int J Pediatr Endocrinol. 2010;2010:275213. doi: 10.1155/2010/275213. Epub 2011 Jan 10. PMID: 21274448; PMCID: PMC3025377.

6. Figueras LM, Pacheco RM, González DG, Domènech MA, Zubicaray BE. Molecular characterization of the new clinical entity associated with congenital adrenal hyperplasia: the CAH-X syndrome in the Spanish population. Adv Lab Med. 2023 Aug 25;4(3):258-267. doi: 10.1515/almed-2023-0071. PMID: 38075167; PMCID: PMC10701499.

7. Vega A, Ocampo J. Prevalencia en Ecuador de hiperplasia suprarrenal congénita detectada mediante la técnica inmunoenzimática umelisa 17OH progesterona neonatal en el proyecto nacional de tamizaje metabólico neonatal. marzo-noviembre 2014. [Tesis de titulación]. Universidad Central del Ecuador 2014. Dspace.uce/3f96ae9a.

8. Merke DP, Auchus RJ. Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. N Engl J Med. 2020 Sep 24;383(13):1248-1261. doi: 10.1056/NEJMra1909786. PMID: 32966723.

9. New MI, Abraham M, Gonzalez B, Dumic M, Razzaghy-Azar M, Chitayat D, Sun L, Zaidi M, Wilson RC, Yuen T. Genotype-phenotype correlation in 1,507 families with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Proc Natl Acad Sci U S A. 2013 Feb 12;110(7):2611-6. doi: 10.1073/pnas.1300057110. Epub 2013 Jan 28. PMID: 23359698; PMCID: PMC3574953.

10. Vidal I, Gorduza DB, Haraux E, Gay CL, Chatelain P, Nicolino M, Mure PY, Mouriquand P. Surgical options in disorders of sex development (dsd) with ambiguous genitalia. Best Pract Res Clin Endocrinol Metab. 2010 Apr;24(2):311-24. doi: 10.1016/j.beem.2009.10.004. PMID: 20541154.

11. Ezquieta B, Cueva E, Oyarzábal M, Oliver A, Varela JM, Jariego C. Gene conversion (655G splicing mutation) and the founder effect (Gln318Stop) contribute to the most frequent severe point mutations in congenital adrenal hyperplasia (21-hydroxylase deficiency) in the Spanish population. Clin Genet. 2002 Aug;62(2):181-8. doi: 10.1034/j.1399-0004.2002.620213.x. PMID: 12220458.

12. Castro PS, Rassi TO, Araujo RF, Pezzuti IL, Rodrigues AS, Bachega TASS, Silva IN. High frequency of nonclassical congenital adrenal hyperplasia form among children with persistently elevated levels of 17-hydroxyprogesterone after newborn screening. J Pediatr Endocrinol Metab. 2019 May 27;32(5):499-504. doi: 10.1515/jpem-2018-0398. PMID: 31028712.

13. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 Nov 1;103(11):4043-4088. doi: 10.1210/jc.2018-01865. Erratum in: J Clin Endocrinol Metab. 2019 Jan 1;104(1):39-40. doi: 10.1210/jc.2018-02371. PMID: 30272171; PMCID: PMC6456929.

14. Sanango W, Gahona J, Perez J Relationship between histopathological patterns with clinical diagnosis in pediatric patients with renal disorders.: A single-center observational study, 4- year follow-up. REV SEN 2022;10(2):82-89. doi: 10.56867/19

Statements

Ethics committee approval and consent to participate

This method is not required for clinical cases.

Consent to publication

The authors have written permission to publish from the patient's guardian.

Conflicts of interest

The research has no financial interests or conflicts of interest.

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