www.tufsteam.com
Innovations in STEAM: Research & Education
ISSN (print): 3105-7071; ISSN (online): 3105-708X
Volume 2; Issue 2; Article No. 24020205
https://doi.org/10.63793/ISRE/0020

CASE REPORT

A Case Report of Non-Classical Congenital Adrenal Hyperplasia of a Two-Year-Old Male Child

Noor Ul Ain, Fakhar Eman, Manahal Amjad
Department of Pharmacology, Government College University, Faisalabad 38000, Pakistan

METADATA

Paper history
Received: 20 November 2023
Revised: 25 April 2024
Accepted: 30 October 2024
Published online: 25 November 2024

Corresponding author
Email:ananoorkhan105@gmail.com
(Noor ul Ain)

Keywords
21-Hydroxylase deficiency
Androgen excess
Precocious puberty
Hydrocortisone therapy

Citation
Noor Ul Ain, Eman, F, Amjad M (2024) A case report of non-classical congenital adrenal hyperplasia of a two-year-old male child. *Innovations in STEAM: Research & Education* 2: 24020205.
https://doi.org/10.63793/ISRE/0020

ABSTRACT

Background: Non-Classical Congenital Adrenal Hyperplasia (NCCAH) is a relatively common autosomal recessive disorder characterized by partial deficiency of 21-hydroxylase enzyme, resulting in excessive adrenal androgen production. The patient history included a high risk of supported pregnancy with growth injections and prior miscarriage.
Objective: This case report presents a rare early-onset of NCCAH in a 2-year-old male child who was brought to the endocrinology emergency department with premature pubic hair development and increased penile length. The objective was to find out the cause of this abnormal condition and find a clinical measure to arrest the condition.
Methodology: Based on clinical features and biochemical findings, a diagnosis of NCCAH was made. Hormonal therapy with oral hydrocortisone was initiated.
Results: Laboratory investigations disclose elevated levels of luteinizing hormones, ACTH, 17-hydroxyprogesterone, progesterone, and testosterone, while other hormonal and imaging studies were within normal range. Hormonal therapy with oral hydrocortisone led to partial improvement in androgen levels over a 3-month follow-up.
Conclusion: This case highlighted the need for early recognition of atypical presentation of NCCAH to prevent complications such as precocious puberty, compromised adult height, and fertility issues by timely therapeutic interventions.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive endocrine condition that affects cortisol production. The syndrome is caused by reduced activity of cortisol-producing enzymes, which results in prolonged adrenocorticotropic hormone (ACTH) stimulation of the adrenal cortex and accumulation of steroid precursors upstream of the enzymatic block (Claahsen-van der Grinten *et al*. 2022). CAH has been separated into classic and non-classic (NC) variants. The current research indicates that polymorphisms in the *CYP21A2* gene and their phenotypic expression are their main cause. In the classic type, enzyme activity is significantly decreased or missing, limiting cortisol production and resulting in newborn symptoms (Claahsen-van der Grinten *et al*. 2022). Non-classic CAH (NCCAH), also known as late-onset CAH, is the most prevalent autosomal recessive endocrine disorder. It is caused by partial 21-hydroxylase activity (about 20–50% of normal), which is adequate to sustain important cortisol and aldosterone activities; thus, hormone replacement is often needed. However, due to low cortisol levels, ACTH secretion is not controlled, resulting in adrenal hyperplasia and hyperandrogenism (Podgórski *et al*. 2018).

Additionally, 21-hydroxylase deficiency accounts for approximately 95% of CAH cases and can present as either the classic (salt-wasting or simple virilizing) or non-classic phenotypes. The remaining cases are primarily caused by 11β-hydroxylase or 3β-hydroxysteroid dehydrogenase deficits, in both classic and non-classic forms. In rare cases, defects in 17α-hydroxylase/17,20-lyase or cholesterol desmolase can lead to serious clinical problems (Piróg *et al*. 2024).

Mutations in *CYP21A2* range from complete loss to partial retention of enzyme function, with the majority resulting from gene conversion events between the functional gene (*CYP21A2*) and its highly similar pseudogene

(*CYP21A1P*). Functional testing show residual activity of 0–5% in severe mutations (Adriaansen *et al*. 2022). According to Kurtoğlu and Hatipoğlu (2017), classical CAH affects 1 in every 15,000–20,000 live births, while NCCAH affects 1 in 200 Caucasians and 1 in 100 of the general population.

The disease is more prevalent among Ashkenazi Jews (1 in 27), Hispanics (~1 in 40), Slavs (1 in 50), and Italians (1 in 300) (Macut *et al*. 2019). According to the original clinical criteria, NCCAH symptoms develop after the age of five years. Females are born without genital ambiguity, but both sexes can develop indications of androgen excess at any time throughout postnatal life. Delayed menarche is prevalent in adolescent females, and secondary amenorrhea can occur in young women (Auer *et al*. 2023).

Female patients may also experience hirsutism, oligomenorrhea, or polycystic ovary, while afflicted males may infrequently present with oligospermia. Untreated people of both sexes may develop small adult height, insulin resistance, and impaired fertility. Boys frequently experience premature pubertal development, precocious puberty, acne, and fast growth. Laboratory results frequently show elevated 17-hydroxyprogesterone, increased ACTH, and excessive luteinizing hormone (LH) release. Genetic testing is recommended for all CAH patients, including parents and siblings. NCCAH patients had an increased risk of testicular adrenal rest tumors, cardiovascular morbidity, and infertility (Muthusamy *et al*. 2010).The treatment of 21-hydroxylase deficiency began in the 1950s. Glucocorticoid replacement therapy restores insufficient cortisol while suppressing excess ACTH, lowering adrenal androgen synthesis. Hydrocortisone is the ideal replacement for 21-OHD, 11β-OHD, and 17α-hydroxylase deficits due to its favorable physiologic profile and lower risk of side effects (Muthusamy *et al*. 2010). The treatment of 21-hydroxylase deficiency began in the 1950s. Glucocorticoid replacement therapy restores insufficient cortisol while suppressing excess ACTH, lowering adrenal androgen synthesis. Hydrocortisone is the ideal replacement for 21-OHD, 11β-OHD, and 17α-hydroxylase deficits due to its favorable physiologic profile and lower risk of side effects (Muthusamy *et al*. 2010).

The medicine is commonly provided orally in divided daily doses (10–20 mg/m²/day) to maintain steady hormone levels and decrease androgens. Families receive emergency injectable hydrocortisone kits (50 mg for youngsters and 100 mg for older people). In situations of poor response, doses may be increased to 20–30 mg/m²/day or switched to more potent, longer-acting synthetic glucocorticoids such as prednisone or dexamethasone; cautious titration is required to avoid overtreatment (Finkielstain *et al*. 2012).

CASE PRESENTATION

Here is a case presentation of 2-year-old child who presented in the emergency to Faisalabad Diabetic and Endocrinology Centre (F-DEC) with the symptoms of pubic hair (4 cm) growth over the last 7 days. Physical examination indicates an

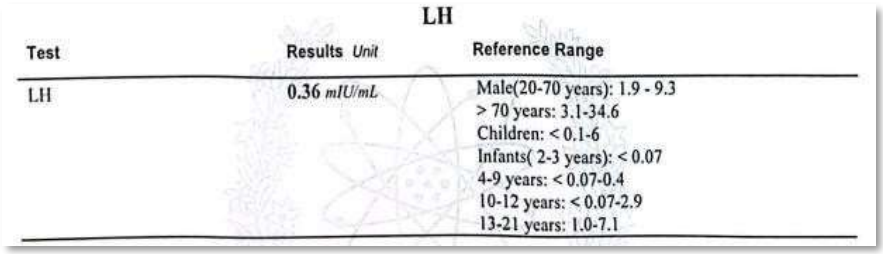
Fig. 1: Growth of pubic hairs (vellus hairs)

Fig. 2: Increased Penile Length

increased penile length of 7 cm that is too high according to his age, and this can be troublesome in the future, because the normal flaccid length in an adult male is 8.7 cm (Fig. 1–17). Clinical findings include the weight of the patient was 14 kg, height was 92 cm, and after laboratory analysis, the patient was diagnosed with non-classical congenital adrenal hyperplasia. There was no family history of any genetic cause; neither the father nor the mother had any disease. However, the mother had one miscarriage before this child during the first trimester, and the cause was unknown. The fetus showed no growth at all, which led to the miscarriage. About seven months later, the mother conceived again, and during the first month of pregnancy, she was given growth-supporting injections of Hydroxyprogesterone Caproate-Estradiol Valerate, four injections in total, administered once a week. This was considered an endangered pregnancy. The patient has eyesight issues, mental health was normal, he was socially active and there is growth of hair on the back of the patient. He was on hormonal therapy, taking Tab Hydrocortisone (10 mg) BD and some multivitamins.

DISCUSSION

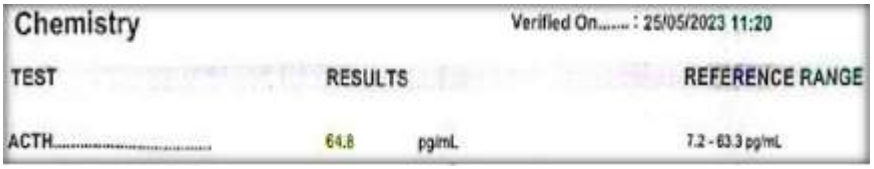
Non-Classical Congenital Adrenal Hyperplasia (NCCAH) is a common autosomal recessive endocrine disorder resulting from partial 21-hydroxylase deficiency. Unlike the classical older children, point to early onset virilization, which can occur even in non-classical form if androgen levels are remarkably high. Such presentations are not common and often overlooked due to the milder nature of NCCAH compared to classical forms. The absence of family history



LH

Test	Results *Unit*	Reference Range
LH	0.36 *mIU/mL*	Male(20-70 years): 1.9 - 9.3 > 70 years: 3.1-34.6 Children: < 0.1-6 Infants(2-3 years): < 0.07 4-9 years: < 0.07-0.4 10-12 years: < 0.07-2.9 13-21 years: 1.0-7.1

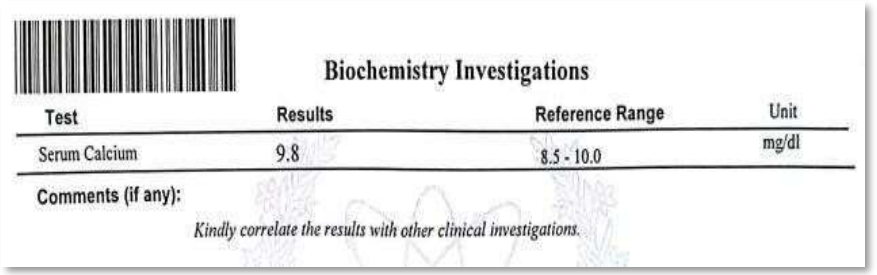
Fig. 3: Showing an elevated level of luteinizing hormone in a patient than normal range



Chemistry — Verified On..... : 25/05/2023 11:20

TEST	RESULTS		REFERENCE RANGE
ACTH.....	64.8	pg/mL	7.2 - 63.3 pg/mL

Fig. 4: Showing elevated level of adreno-corticotropic hormone



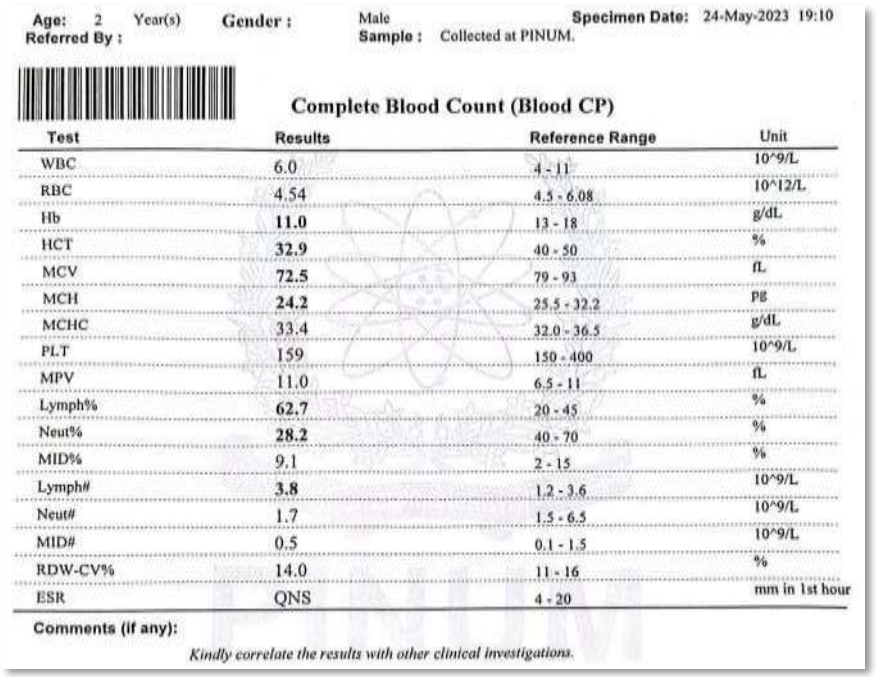
Biochemistry Investigations

Test	Results	Reference Range	Unit
Serum Calcium	9.8	8.5 - 10.0	mg/dl

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 5: Normal serum calcium level



Age: 2 Year(s) Gender : Male Specimen Date: 24-May-2023 19:10
Referred By : Sample : Collected at PINUM.

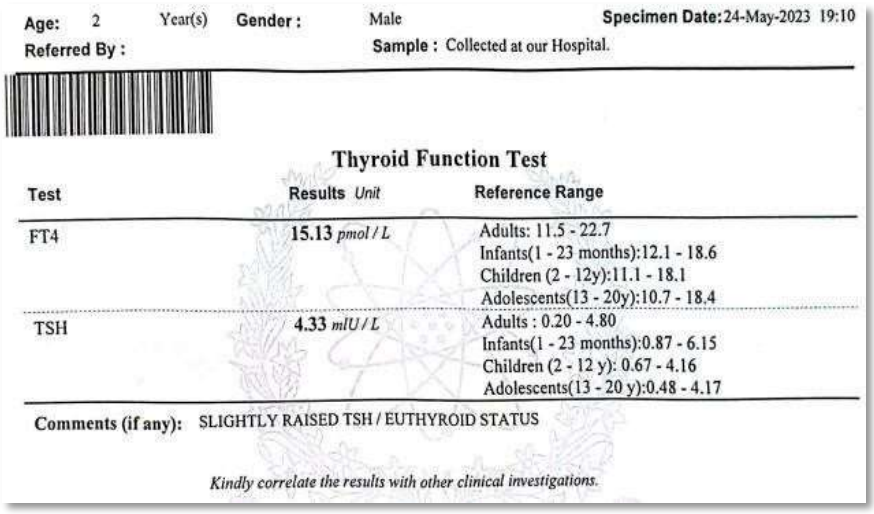
Complete Blood Count (Blood CP)

Test	Results	Reference Range	Unit
WBC	6.0	4 - 11	10^9/L
RBC	4.54	4.5 - 6.08	10^12/L
Hb	**11.0**	13 - 18	g/dL
HCT	**32.9**	40 - 50	%
MCV	**72.5**	79 - 93	fL
MCH	**24.2**	25.5 - 32.2	pg
MCHC	33.4	32.0 - 36.5	g/dL
PLT	159	150 - 400	10^9/L
MPV	11.0	6.5 - 11	fL
Lymph%	**62.7**	20 - 45	%
Neut%	**28.2**	40 - 70	%
MID%	9.1	2 - 15	%
Lymph#	**3.8**	1.2 - 3.6	10^9/L
Neut#	1.7	1.5 - 6.5	10^9/L
MID#	0.5	0.1 - 1.5	10^9/L
RDW-CV%	14.0	11 - 16	%
ESR	QNS	4 - 20	mm in 1st hour

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 6: Complete blood count (CBC) analysis of the patient



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

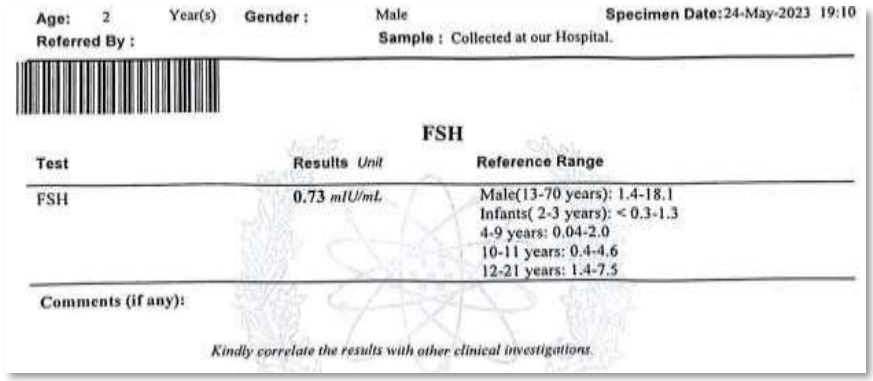
Thyroid Function Test

Test	Results *Unit*	Reference Range
FT4	**15.13** *pmol / L*	Adults: 11.5 - 22.7 Infants(1 - 23 months):12.1 - 18.6 Children (2 - 12y):11.1 - 18.1 Adolescents(13 - 20y):10.7 - 18.4
TSH	**4.33** *mIU / L*	Adults : 0.20 - 4.80 Infants(1 - 23 months):0.87 - 6.15 Children (2 - 12 y): 0.67 - 4.16 Adolescents(13 - 20 y):0.48 - 4.17

Comments (if any): SLIGHTLY RAISED TSH / EUTHYROID STATUS

Kindly correlate the results with other clinical investigations.

Fig. 7: Thyroid function test, indicating normal level of Free Thyroxin 4 (FT4) and milder elevated level of Thyroid Stimulating Hormone (TSH) in infants



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

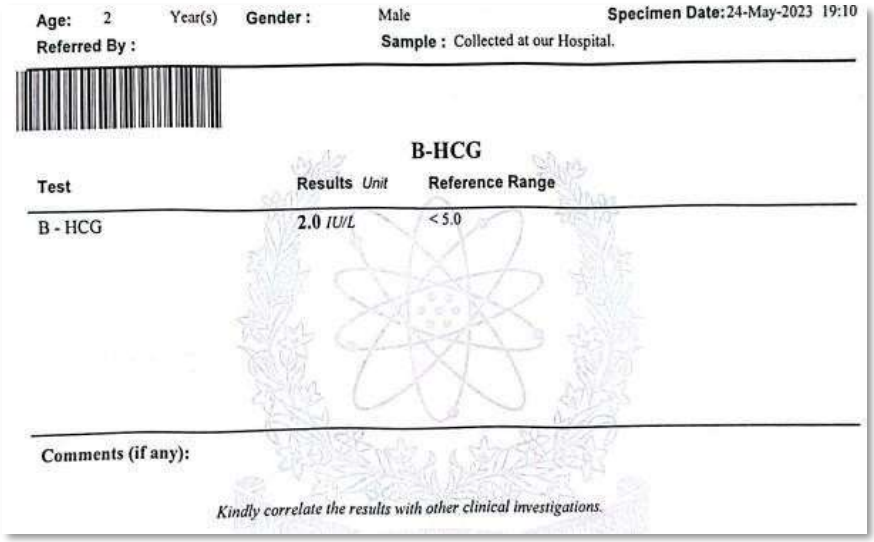
FSH

Test	Results *Unit*	Reference Range
FSH	**0.73** *mIU/mL*	Male(13-70 years): 1.4-18.1 Infants(2-3 years): < 0.3-1.3 4-9 years: 0.04-2.0 10-11 years: 0.4-4.6 12-21 years: 1.4-7.5

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 8: Showing normal range of follicle follicle-stimulating hormone (FSH) in infants



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

B-HCG

Test	Results *Unit*	Reference Range
B - HCG	**2.0** *IU/L*	< 5.0

Comments (if any):

Kindly correlate the results with other clinical investigations.

Fig. 9: Lab analysis showing normal value of Beta-human Chronic Gonadotropin in Patient

Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

Progesterone

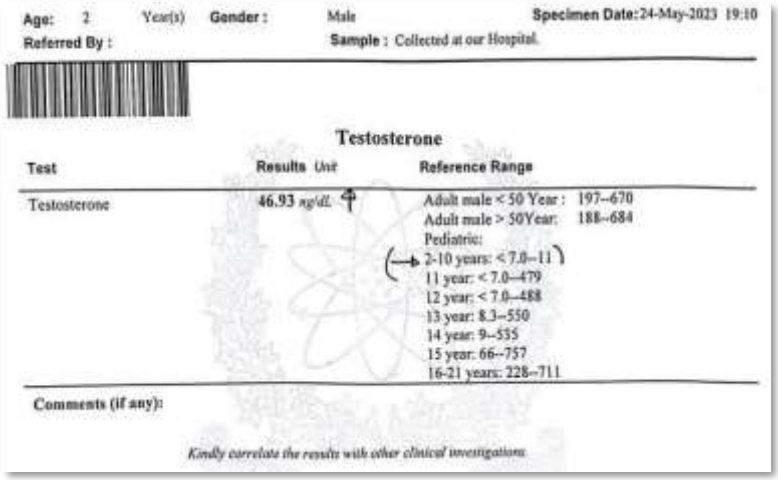
Test	Results Unit	Reference Range
Progesterone	11.23 ng/mL	0.28 - 1.22

Comments (if any):

Kindly correlate the results with other clinical investigations

17-oH-progesterone

Fig.10: Lab analysis shows an elevated level of progesterone analysis shows an elevated level of progesterone



Age: 2 Year(s) Gender : Male Specimen Date:24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

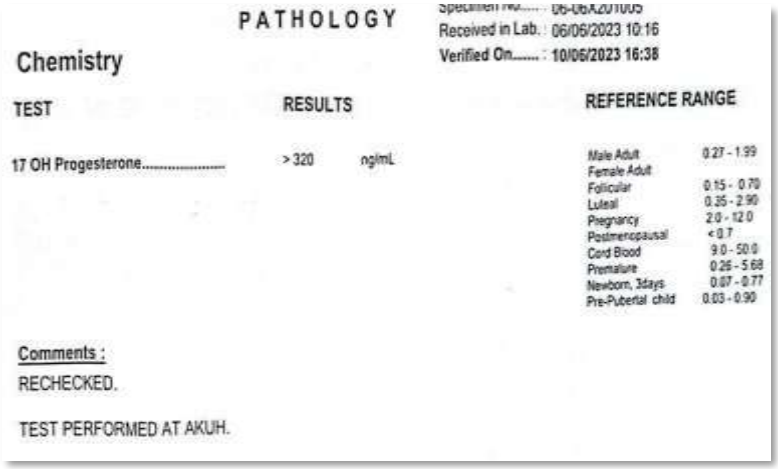
Testosterone

Test	Results Unit	Reference Range
Testosterone	46.93 ng/dL	Adult male < 50 Year : 197--670 Adult male > 50Year: 188--684 Pediatric: 2-10 years: < 7.0--11 11 year: < 7.0--479 12 year: < 7.0--488 13 year: 8.3--550 14 year: 9--535 15 year: 66--757 16-21 years: 228--711

Comments (if any):

Kindly correlate the results with other clinical investigations

Fig. 11: Lab analysis shows an elevated level of testosterone



PATHOLOGY

Specimen Rec..... : 06-06A201005
Received in Lab. : 06/06/2023 10:16
Verified On..... : 10/06/2023 16:38

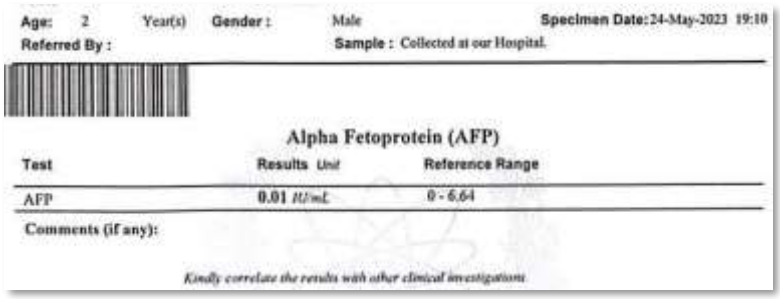
Chemistry

TEST	RESULTS		REFERENCE RANGE	
17 OH Progesterone.....	> 320	ng/mL	Male Adult	0.27 - 1.99
			Female Adult	
			Follicular	0.15 - 0.70
			Luteal	0.35 - 2.90
			Pregnancy	2.0 - 12.0
			Postmenopausal	< 0.7
			Cord Blood	9.0 - 50.0
			Premature	0.26 - 5.68
			Newborn, 3days	0.07 - 0.77
			Pre-Pubertal child	0.03 - 0.90

Comments :
RECHECKED.

TEST PERFORMED AT AKUH.

Fig. 12: Lab analysis shows an increased level of 17-hydroxy progesterone



Age: 2 Year(s) Gender : Male Specimen Date: 24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

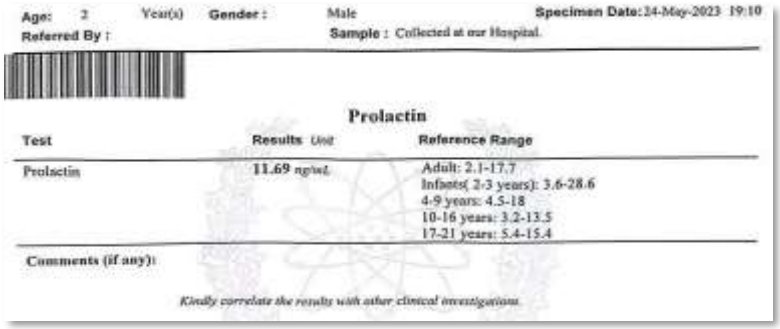
Alpha Fetoprotein (AFP)

Test	Results Unit	Reference Range
AFP	0.01 IU/mL	0 - 6.64

Comments (if any):

Kindly correlate the results with other clinical investigations

Fig. 13: Lab analysis shows normal level of alpha fetoprotein



Age: 2 Year(s) Gender : Male Specimen Date: 24-May-2023 19:10
Referred By : Sample : Collected at our Hospital.

Prolactin

Test	Results Unit	Reference Range
Prolactin	11.69 ng/mL	Adult: 2.1-17.7 Infants(2-3 years): 3.6-28.6 4-9 years: 4.5-18 10-16 years: 3.2-13.5 17-21 years: 5.4-15.4

Comments (if any):

Kindly correlate the results with other clinical investigations

Fig. 14: Normal range of prolactin hormone in patient

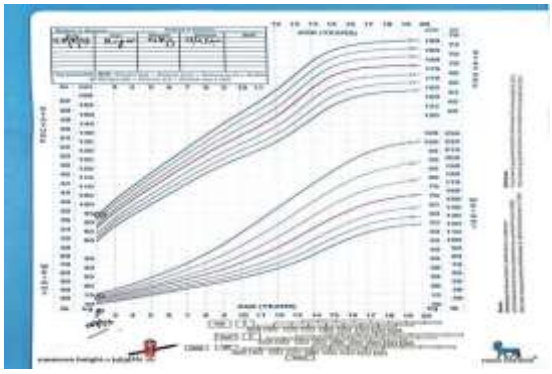


Fig. 15: Growth chart indicates height and weight relation

SCROTAL DOPPLER ULTRASOUND

Right testicle measures Volume 0.9ml
Left testicle measures Volume 1.0ml

Both testes are normal sized showing homogenous parenchyma and smooth contours. No focal mass lesion seen on either side.
Doppler indices of parenchymal arteries are normal.

Epididymii are of normal size and echotexture.

No hydrocele seen on either side. Scrotal wall is normal.
Both pampiniform plexus are unremarkable. No dilated venous plexus are appreciated on either side.

IMPRESSION:

- **Unremarkable Doppler Study**

Dr Hassan Bukhari

Fig. 16: Ultrasound report of the Scrotum region in the patient

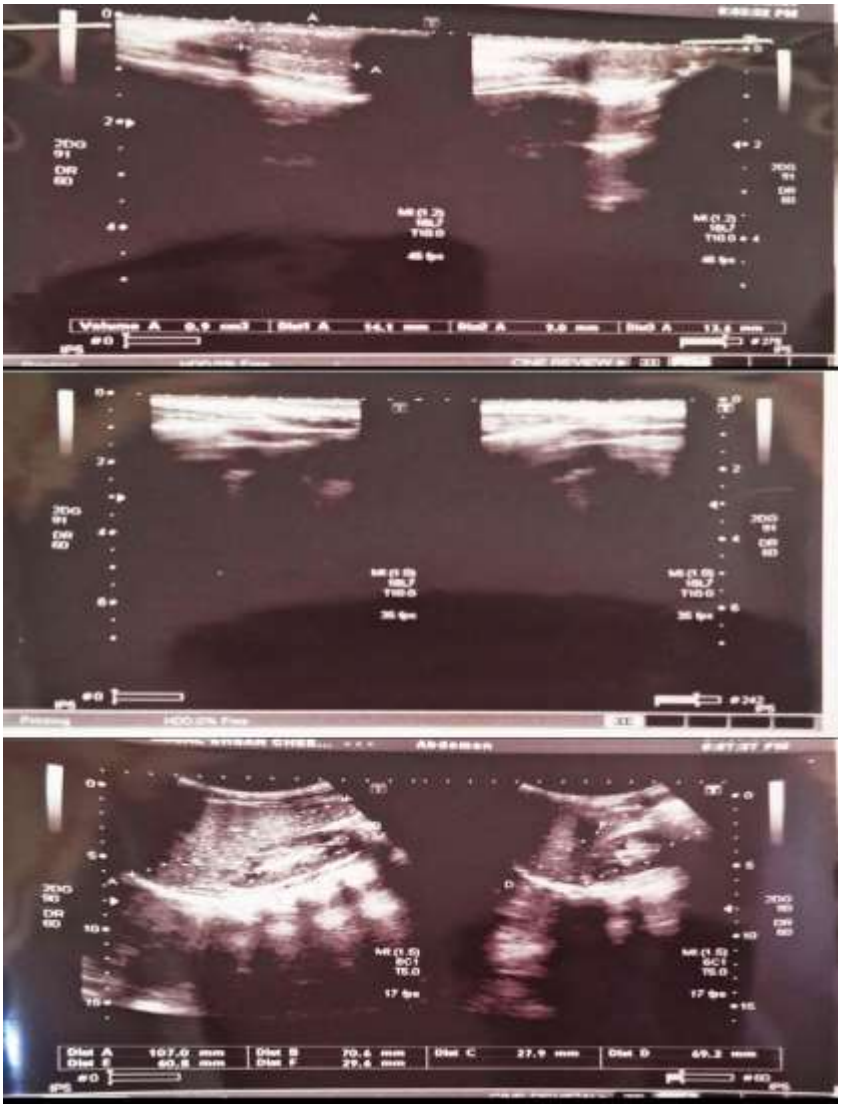


Fig. 17: Ultrasound image of the scrotum region in the patient

and the normal health status of both parents suggests a *de novo* carrier, indicating mutation or a recessive carrier state in one or both parents, which is consistent with an autosomal recessive inheritance pattern on CAH. The history of unexplained miscarriage in the first trimester may be coincidental, but it also raises the possibility of a previously affected fetus with a more severe phenotype or chromosomal abnormality (Finkielstain *et al*. 2012).

The administration of Hydroxyprogesterone Caproate and Estradiol Valerate during early pregnancy may have supported the gestation in this case, especially since it was labelled as an endangered pregnancy. However, there is limited evidence on whether these hormonal injections have any direct influence on fetal adrenal gland development. Elevated androgen levels in NCCAH result from partial 21-hydroxylase deficiency, leading to build-up of 17-OH progesterone and other precursors. In this case, early hormonal therapy with hydrocortisone has been initiated, which is recommended as first-line treatment to reduce ACTH secretion and adrenal androgen production. The psychosocial and physical impact of such early symptoms can be significant; hence, timely diagnosis and management are crucial (Auer *et al*. 2023). This case highlights the importance of considering NCCAH in the differential diagnosis of premature pubarche, even in the absence of a family history. It also points out the role of detailed perinatal history and early endocrinology evaluation in patients presenting with signs of androgen excess (Auchus and Arlt 2013).

AUTHOR CONTRIBUTIONS

Noor ul Ain designed and supervised the research and final draft of the manuscript; Fakhar Eman and Manahal Amjad completed the research, assisted in write-up, rephrasing, and

final draft preparation.

DATA AVAILABILITY

The data will be made available on a fair request.

ETHICS APPROVAL

Informed consent was obtained from the patient's family.

FUNDING SOURCE

This project is not funded by any agency.

REFERENCES

Adriaansen BP, Schröder MA, Span PN, Sweep FC, van Herwaarden AE, Claahsen-van der Grinten HL (2022) Challenges in treatment of patients with non-classic congenital adrenal hyperplasia. *Frontiers in Endocrinology* 13: 1064024. https://doi.org/10.3389/fendo.2022.1064024.

Auchus RJ, Arlt W (2013) Approach to the patient: the adult with congenital adrenal hyperplasia. *The Journal of Clinical Endocrinology & Metabolism* 98: 2645–2655. https://doi.org/10.1210/jc.2013-1440.

Auer MK, Nordenström A, Lajic S, Reisch N (2023) Congenital adrenal hyperplasia. *Lancet* 401: 227–244. https://doi.org/110.1016/S0140-6736(22)01330-7.

Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, Arlt W, Auchus RJ, Falhammar H, Flück CE, Guasti L, Huebner A, Kortmann BB (2022) Congenital adrenal hyperplasia—current insights in pathophysiology, diagnostics, and management. *Endocrine Reviews* 43: 91–159. https://doi.org/10.1210/endrev/bnab016.

Finkielstain GP, Kim MS, Sinaii N, Nishitani M, Van Ryzin C, Hill SC, Reynolds JC, Hanna RM, Merke DP (2012) Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. *The Journal of Clinical Endocrinology & Metabolism* 97: 4429–4438. https://doi.org/10.1210/jc.2012-2102.

Kurtoğlu S, Hatipoğlu N (2017) Non-classical congenital adrenal hyperplasia in childhood. *Journal of Clinical Research in Pediatric Endocrinology* 9: 1–8. https://doi.org/10.4274/jcrpe.3378.

Macut D, Zdravković V, Bjekić-Macut J, Mastorakos G, Pignatelli D (2019) Metabolic perspectives for non-classical congenital adrenal hyperplasia with relation to the classical form of the disease. *Frontiers in Endocrinology* 10: 681. https://doi.org/10.3389/fendo.2019.00681.

Muthusamy K, Elamin MB, Smushkin G, Murad MH, Lampropulos JF, Elamin KB, Abu Elnour NO, Gallegos-Orozco JF, Fatourechi MM, Agrwal N (2010) Adult height in patients with congenital adrenal hyperplasia: a systematic review and meta-analysis. *The Journal of Clinical Endocrinology & Metabolism* 95: 4161–4172. https://doi.org/10.1210/jc.2009-2616.

Piróg M, Pulka A, Zabiegło E, Jach R (2024) Nonclassical congenital adrenal hyperplasia: Metabolic and hormonal profile. *Clinical Endocrinology* 100: 109–115. https://doi.org/10.1111/cen.14988.

Podgórski R, Aebisher DA, Stompor M, Podgórska D, Mazur A (2018) Congenital adrenal hyperplasia: clinical symptoms and diagnostic methods. *Acta Biochimica Polonica* 65: 25–33. https://doi.org/10.18388/abp.2017_2343.