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THE SPECTRUM OF METABOLIC COMPLICATIONS IN CHILDREN AND ADOLESCENTS WITH CONGENITAL ADRENAL HYPERPLASIA PRESENTING IN TERTIARY CARE HOSPITAL

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Abstract

Objective: To determine the prevalence and spectrum of metabolic complications among children and adolescents with congenital adrenal hyperplasia (CAH)
Methods: This cross-sectional study was conducted at the Department of Paediatric Endocrinology, The Children's Hospital and University of Child Health Sciences, Lahore, Pakistan from February 2025 to August 2025. Twenty-nine children and adolescents aged 7–18 years with classic CAH receiving regular follow-up were enrolled. Anthropometric measurements, blood pressure, waist circumference, fasting blood glucose, fasting insulin, lipid profile, liver enzymes, abdominal ultrasonography, echocardiography, and serum 17-hydroxyprogesterone levels were assessed.
Results: Twenty-nine patients were included, comprising 17 (58.6%) females and 12 (41.4%) males. Salt-wasting CAH was present in 24 (82.8%) patients, while 5 (17.2%) had the simple virilizing form. Only 8 (27.6%) patients achieved good biochemical disease control. Short stature observed in 12 (41.3%) was most common complication followed by Insulin resistance as the most common metabolic abnormality, affecting 8 (27.6%) participants, followed by dyslipidemia in 5 (17.2%), hypertension in 4 (13.8%), obesity in 7 (24.1%), impaired fasting glucose in 2 (6.9%), and non-alcoholic fatty liver disease in 1 (3.4%). Among female participants, hirsutism was the most common hyperandrogenic manifestation, affecting 9 (52.9%), followed by menstrual irregularities in 6 (35.3%), Two (11.8%) fulfilled the diagnostic criteria for polycystic ovary syndrome(PCOS).
Conclusion: Metabolic complications are common among children and adolescents with CAH, withshort stature and insulin resistance being the predominant one.

Keywords: Congenital adrenal hyperplasia, insulin resistance, dyslipidemia, obesity, hypertension, metabolic complications, children, adolescents.

Introduction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders characterized by impaired adrenal steroidogenesis, with approximately 95% of cases resulting from 21-hydroxylase deficiency caused by pathogenic variants in the CYP21A2 gene. Deficient cortisol synthesis leads to chronic elevation of adrenocorticotropic hormone (ACTH), resulting in adrenal hyperplasia and excessive adrenal androgen production. Depending on the severity of enzyme deficiency, classic CAH presents as either the salt-wasting or simple virilizing form and requires lifelong glucocorticoid replacement, with mineralocorticoid therapy in patients with salt-wasting

disease. Advances in neonatal diagnosis and improved treatment have substantially increased survival, shifting the focus of care from preventing adrenal crises to optimizing long-term health outcomes and quality of life.[1–3]

Despite improved survival, children and adolescents with CAH remain at increased risk of developing metabolic and cardiovascular complications. Multiple factors contribute to this risk, including chronic glucocorticoid exposure, hyperandrogenism, altered body composition, reduced insulin sensitivity, and persistent hormonal imbalance resulting from suboptimal disease control. Both overtreatment and undertreatment may adversely affect growth, pubertal development, and metabolic health. Consequently, obesity, hypertension, dyslipidaemia, insulin resistance, impaired glucose metabolism, non-alcoholic fatty liver disease (NAFLD), and early cardiovascular abnormalities have emerged as important long-term complications in this population.[1–6]

Recent studies have demonstrated that these metabolic abnormalities may become evident during childhood and adolescence, well before adulthood. A comprehensive review by Panic Zaric et al. highlighted that insulin resistance, obesity, dyslipidaemia, hypertension, and increased cardiovascular risk are increasingly recognized in pediatric patients with classic CAH.[4] Similarly, Barbot et al. reported that chronic glucocorticoid therapy and persistent hormonal imbalance contribute significantly to metabolic syndrome and cardiovascular morbidity in affected individuals.[5] Meguid et al. demonstrated that components of metabolic syndrome, particularly obesity and insulin resistance, may be present even in young children with classic CAH receiving corticosteroid therapy.[6] Furthermore, Kim et al. reported a higher prevalence of obesity, increased waist circumference, insulin resistance, and dyslipidaemia among children and adolescents with classic CAH compared with healthy peers, emphasizing the importance of regular metabolic surveillance from an early age.[8]

Although several studies from Pakistan have described the clinical presentation and management challenges of CAH, comprehensive data regarding long-term metabolic complications remain limited. A recent review by Mansoor et al. summarized the clinical spectrum of CAH in Pakistani children and highlighted the challenges posed by delayed diagnosis, lack of newborn screening, and limited local evidence regarding long-term outcomes.[9] Similarly, a cross-sectional study from Karachi evaluated growth characteristics in children with CAH but did not comprehensively assess metabolic abnormalities such as insulin resistance, dyslipidaemia, hypertension, NAFLD, or cardiovascular risk.[10] Therefore, evidence regarding the spectrum of metabolic complications among Pakistani children and adolescents with CAH remains scarce.

Objective

The present study was conducted to determine the spectrum of metabolic complications among children and adolescents with congenital adrenal hyperplasia attending a tertiary care hospital and to evaluate their association with clinical characteristics and biochemical disease control.

Methodology

This cross-sectional observational study was conducted in the Department of Paediatric Endocrinology and Diabetes, University of Child Health Sciences and The Children's Hospital, Lahore from February 2025 to August 2025 following approval by the Institutional Review Board (IRB). Children and adolescents aged 7–18 years with confirmed diagnosis of congenital adrenal hyperplasia (salt wasting and simple virilizing forms) receiving regular follow-up and treatment at our center were included in the study while those with chronic diseases or congenital defects, syndromes or genetic conditions that can affect the metabolic outcomes, with missing or insufficient clinical and laboratory data and who didn't give consent were excluded. Total 29 patients were enrolled using non-probability consecutive sampling techniques.

Data Collection

After obtaining informed consent, demographic and clinical information, including age, sex, age at presentation and diagnosis, disease duration, treatment details, and family history, was recorded using a structured proforma. Anthropometric measurements including height, weight, body mass index (BMI), waist circumference, and blood pressure were measured using standardized techniques. Laboratory investigations included fasting blood glucose, HbA1c, fasting insulin , lipid profile, ALT, 17-hydroxyprogesterone ,LH,FSH testosterone (where applicable), ultrasound abdomen and Echocardiography were assessed .Metabolic complications including obesity, hypertension, dyslipidemia, insulin resistance, impaired glucose metabolism/diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, polycystic ovary syndrome, menstrual irregularities, and left ventricular dysfunction were evaluated according to the operational definitions .

Statistical Analysis

Statistical Analysis Data were entered and analyzed using IBM SPSS 25**.** Continuous variables were assessed for normality using the Shapiro–Wilk test and are presented as mean ± standard deviation (SD)**.** Categorical variables are presented as frequencies and percentages. Comparisons between two independent groups were performed using the independent-samples t-test for continuous variables and the Chi-square test **or** Fisher's exact test, as appropriate, for categorical variables. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Result

A total of 29 children and adolescents with congenital adrenal hyperplasia (CAH) were included in the study, comprising 17 (58.6%) females and 12 (41.4%) males. The majority had the salt-wasting subtype (24, 82.8%), while 5 (17.2%) had simple virilizing CAH. The mean age at presentation was 2.15 ± 3.36 years, and the mean age at diagnosis was 2.18 ± 3.31 years. Disease duration ranged from 1 to 17 years. Based on serum 17-hydroxyprogesterone (17-OHP) levels, only 8 (27.6%) patients achieved good biochemical disease control, whereas 21 (72.4%) had poor disease control. The mean current hydrocortisone dose was 17.3 ± 3.4 mg/m²/day, and only one patient had received prednisolone therapy (Table 1).

Table 1. Baseline demographic and clinical characteristics of study participants (n = 29)

Complication	Definition	n (%)
Growth		
Short stature	Height <3rd percentile	12 (41.3)
Obesity-related		
Obesity	BMI ≥95th percentile	7 (24.1)
Central adiposity	Waist circumference >90th percentile	1 (3.4)
Blood pressure		
Hypertension	BP ≥95th percentile	4 (13.8)
Glucose metabolism		
Impaired fasting glucose	FBS 100–125 mg/dL	2 (6.9)
Diabetes Mellitus	As per operational definition	0
Elevated fasting insulin	Above reference range	12 (41.4)
Insulin resistance	HOMA-IR above age- and sex-specific cutoff	8 (27.6)
Acanthosis nigricans	Clinical examination	8 (27.6)
Lipid abnormalities	Dyslipidaemia criteria	5 (17.2)
Liver involvement		
Elevated ALT	Age- and sex-specific cut-off	4 (13.8)
Grade I fatty liver	Ultrasound	5 (17.2)
NAFLD	Fatty liver + elevated ALT	1 (3.4)
Cardiovascular		
Mild LVH	Echocardiography	2 (6.9)
Hyperandrogenism (Females, n=17)		
Hirsutism	Ferriman–Gallwey score ≥8	9 (52.9)
Mild acne	Clinical assessment	4 (23.5)
Moderate acne	Clinical assessment	3 (17.6)
Menstrual irregularities	As per defined criteria	6 (35.3)
Primary amenorrhoea		1 (5.9)
Secondary amenorrhoea		1 (5.9)
Oligomenorrhoea		4 (23.5)
PCOS	As per criteria	2 (11.8)
Metabolic syndrome	Weiss et al criteria	0

The most frequent clinical and metabolic complication was short stature, affecting 12 (41.3%) patients. Obesity was present in 7 (24.1%), while central adiposity reflected by waist circumference was identified in only one (3.4%) patient. Hypertension was observed in 4 (13.8%) patients. Elevated fasting insulin was detected in 12 (41.4%), whereas insulin resistance based on HOMA-IR was present in 8 (27.6%), accompanied by acanthosis nigricans in 8 (27.6%) patients. Impaired fasting glucose was identified in 2 (6.9%) patients, and none fulfilled the diagnostic criteria for

metabolic syndrome. Dyslipidaemia was present in 5 (17.2%) patients. Liver involvement included grade I fatty liver in 5 (17.2%), elevated ALT in 4 (13.8%), and NAFLD in one (3.4%) male adolescent. Echocardiography demonstrated mild left ventricular hypertrophy in 2 (6.9%) patients. Among female participants, hirsutism was the most common hyperandrogenic manifestation, affecting 9 (52.9%), followed by menstrual irregularities in 6 (35.3%), including primary amenorrhoea in one, secondary amenorrhoea in one, and oligomenorrhoea in four patients. Two (11.8%) females fulfilled the diagnostic criteria for polycystic ovary syndrome (Table 2).

Table 2. Clinical and metabolic complications in children and adolescents with congenital adrenal hyperplasia (n = 29

Variable	Male (n=12)	Female (n=17)	P value
Short stature	5 (41.7)	7 (41.2)	1.00
Obesity	2 (16.7)	5 (29.4)	0.67
Hypertension	1 (8.3)	3 (17.6)	0.63
Impaired fasting glucose	1 (8.3)	1 (5.9)	1.00
Elevated fasting insulin	4 (33.3)	8 (47.1)	0.47
Insulin resistance	2 (16.7)	6 (35.3)	0.42
Acanthosis nigricans	3 (25.0)	5 (29.4)	1.00
Dyslipidaemia	1 (8.3)	4 (23.5)	0.36
Elevated ALT	2 (16.7)	2 (11.8)	1.00
Grade I fatty liver	3 (25.0)	2 (11.8)	0.37
NAFLD	1 (8.3)	0	0.41

Discussion

The present study evaluated the spectrum of metabolic complications among children and adolescents with congenital adrenal hyperplasia (CAH) attending a tertiary care hospital in Pakistan. Insulin resistance was the most frequently observed metabolic abnormality, followed by dyslipidemia and hypertension, whereas diabetes mellitus and metabolic syndrome were not identified. Although females demonstrated a higher numerical prevalence of metabolic complications than males, these differences were not statistically significant. Furthermore, only 27.6% of patients achieved good biochemical disease control, highlighting the challenges of optimizing long-term management in pediatric CAH.

Insulin resistance was identified in more than one-quarter of the study population based on age- and pubertal stage-specific HOMA-IR cut-offs and represented the commonest metabolic abnormality in our cohort. Similar findings have been reported in previous pediatric studies, where insulin resistance is consistently recognized as one of the earliest manifestations of metabolic dysfunction in CAH.[4,6,8,12,14] Dyslipidemia and hypertension were observed in 17.2% and 13.8% of participants, respectively, comparable to previous reports in children with CAH.[4,5,8,12,15] These abnormalities are likely multifactorial, resulting from chronic glucocorticoid therapy, increased adiposity, insulin resistance, and persistent hormonal imbalance.[1,2,5] Although only one participant fulfilled the diagnostic criteria for non-alcoholic fatty liver disease (NAFLD), five patients demonstrated grade 1 hepatic steatosis on ultrasonography and four had elevated alanine aminotransferase levels according to age- and sex-specific cut-offs. These findings suggest that hepatic involvement may begin during childhood before the development of established NAFLD.[4,5,22]

The prevalence of obesity in our cohort was lower than that reported in several international studies.[4,6,8,15,16] Differences in ethnicity, dietary habits, physical activity, socioeconomic factors, and treatment practices may partly explain these variations. Nevertheless, excess adiposity remains clinically important because increasing body mass index contributes to worsening insulin resistance and future cardiovascular risk.[1,4,5] In our cohort, central adiposity was uncommon; however, insulin resistance was observed even in the absence of marked obesity, suggesting that factors beyond adiposity, including glucocorticoid exposure and disease-related hormonal disturbances, contribute to metabolic dysfunction. Females demonstrated a higher numerical prevalence of insulin resistance, dyslipidemia, hypertension, hirsutism, menstrual irregularities, and polycystic ovary syndrome (PCOS), although none of these differences reached statistical significance. Hyperandrogenism combined with prolonged glucocorticoid exposure may predispose females with CAH to metabolic disturbances resembling those observed in adolescents with PCOS.[20,21] The lack of statistically significant sex differences in the present study is likely attributable to the relatively small sample size and should be explored further in larger multicentre studies. Published data regarding metabolic outcomes among Pakistani children with CAH remain limited. Previous local studies have primarily focused on the clinical spectrum of disease, growth characteristics, and vitamin D status rather than comprehensive metabolic assessment.[9,10,23] To our knowledge, this is among the first Pakistani studies to comprehensively evaluate metabolic

complications, including insulin resistance, dyslipidemia, hypertension, obesity, hepatic involvement, and biochemical disease control in children and adolescents with CAH.

Conclusion

Children and adolescents with congenital adrenal hyperplasia exhibited a considerable burden of metabolic abnormalities, with short stature and insulin resistance being the most frequent complications, followed by dyslipidemia and hypertension. Most patients had poor biochemical disease control, and metabolic abnormalities were predominantly observed among those with longer disease duration. Although females demonstrated a higher numerical prevalence of metabolic complications, gender-based differences were not statistically significant.

Author contribution

Bushra Naseer Khan: Collected clinical data, wrote the manuscript.
Sommayya Aftab: Performed the literature review
Nida Aslam: Helped in finalizing manuscript.
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Acknowledgement

Dr Qaiser Mehmood
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Ethical Considerations

Ethical approval was obtained from the Institutional Review Board of the University of Child Health Sciences and The Children's Hospital, Lahore. Written informed consent was obtained from parents ,legal guardians before enrolment and from older children whenever was appropriate. Confidentiality of participants was maintained by anonymizing all collected data

Conflict of Interest

None to Declare

References

1. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, Arlt W, Auchus RJ, Falhammar H, et al. Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. Endocr Rev. 2022;43(1):91-159.
2. Auer MK, Nordenström A, Lajic S, Reisch N. Congenital adrenal hyperplasia. Lancet. 2023;401(10372):227-244.
3. Fraga NR, Minaeian N, Kim MS. Congenital adrenal hyperplasia. Pediatr Rev. 2024;45(2):74-84.
4. Panic Zaric S, Milenkovic T, Todorovic S, Mitrovic K, Cvetkovic D, Cehic M, et al. Metabolic syndrome spectrum in children with classic congenital adrenal hyperplasia: a comprehensive review. Metabolites. 2025;15(2):89.
5. Barbot M, Mazzeo P, Lazzara M, Ceccato F, Scaroni C. Metabolic syndrome and cardiovascular morbidity in patients with congenital adrenal hyperplasia. Front Endocrinol (Lausanne). 2022;13:934675.
6. Meguid SE, Soliman AT, De Sanctis V, Abougabal AM, Ramadan MA, Hassan M, et al. Growth and metabolic syndrome criteria in young children with classic congenital adrenal hyperplasia treated with corticosteroids. Acta Biomed. 2022;93(5):e2022304.
7. Pijnenburg-Kleizen KJ, Thomas CM, Otten BJ, Roeleveld N, Claahsen-van der Grinten HL. Long-term follow-up of children with classic congenital adrenal hyperplasia: suggestions for age-dependent treatment in childhood and puberty. J Pediatr Endocrinol Metab. 2019;32(10):1055-1063.
8. Kim MS, Fraga NR, Minaeian N, Geffner ME. Components of metabolic syndrome in youth with classical congenital adrenal hyperplasia. Front Endocrinol (Lausanne). 2022;13:848274.

9. Mansoor S, Baloch MH, Khan Z, Ashraf A. A clinical account of Pakistani children suffering from congenital adrenal hyperplasia. J Pak Med Assoc. 2023;73(2):366-369.
10. Qayyum A, Rai VR, Memon R, Mahar S, Laghari TM, Ibrahim MN. Growth characteristics in children with congenital adrenal hyperplasia visiting a tertiary care hospital in Karachi. Pak Armed Forces Med J. 2023;73(1):96.
11. Bacila I, Lawrence NR, Mahdi S, Alvi S, Cheetham TD, Crowne E, et al. Health status of children and young persons with congenital adrenal hyperplasia in the UK: a cross-sectional multicentre study. Eur J Endocrinol. 2022;187(4):543-553.
12. Improda N, Barbieri F, Ciccarelli GP, Capalbo D, Salerno M. Cardiovascular health in children and adolescents with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Front Endocrinol (Lausanne). 2019;10:212.
13. Pofi R, Ji X, Krone NP, Tomlinson JW. Long-term health consequences of congenital adrenal hyperplasia. Clin Endocrinol (Oxf). 2024;101(4):318-331.
14. Vijayan R, Bhavani N, Pavithran PV, Nair V, Menon UV, Menon AS, et al. Metabolic profile, cardiovascular risk factors and health-related quality of life in children, adolescents and young adults with congenital adrenal hyperplasia. J Pediatr Endocrinol Metab. 2019;32(8):871-877.
15. Mooij CF, van Herwaarden AE, Sweep FC, Roeleveld N, de Korte CL, Kapusta L, et al. Cardiovascular and metabolic risk in pediatric patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Pediatr Endocrinol Metab. 2017;30(9):957-966.
16. Ben Simon A, Brener A, Segev-Becker A, Yackobovitch-Gavan M, Uretzky A, Schachter Davidov A, et al. Body composition in children and adolescents with non-classic congenital adrenal hyperplasia and the risk for components of metabolic syndrome: an observational study. Front Endocrinol (Lausanne). 2022;13:1022752.
17. Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. J Clin Res Pediatr Endocrinol. 2010;2(3):100-106.
18. Nielsen TR, Lausten-Thomsen U, Fonvig CE, Bøjsøe C, Pedersen L, Bratholm PS, et al. Dyslipidemia and reference values for fasting plasma lipid concentrations in Danish/North-European White children and adolescents. BMC Pediatr. 2017;17:116.
19. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350(23):2362-2374.
20. Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med. 2020;18:72.
21. Kamboj MK, Bonny AE. Polycystic ovary syndrome in adolescence: diagnostic and therapeutic strategies. Transl Pediatr. 2017;6(4):248-255.
22. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the Expert Committee on NAFLD and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2017;64(2):319-334.
23. Jamali AA, Fatima S, Raza SJ, Kayani A, Siddiqui QU. Vitamin D deficiency in children with congenital adrenal hyperplasia: a cross-sectional study from a tertiary healthcare centre in Pakistan. Pak Pediatr J. 2024;48(4).