CLINICAL AND THERAPEUTIC FACTORS ASSOCIATED WITH DYSLIPIDEMIA IN CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA

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Dyslipidemia is increasingly recognized as a metabolic complication in children with congenital adrenal hyperplasia (CAH), yet the associated clinical and treatment-related factors remain incompletely understood. This study aimed to identify the clinical and therapeutic factors associated with dyslipidemia in children with CAH. We conducted a cross-sectional study on 73 patients with CAH (aged 1–17 years old) at the Vietnam National Children's Hospital. Data on anthropometrics, clinical signs (acanthosis nigricans, Cushing's syndrome), duration of glucocorticoid and fludrocortisone therapy, and lipid profiles were collected. The results showed that acanthosis nigricans was significantly associated with LDL-C dyslipidemia (p = 0.016). Cushing's syndrome showed a similar trend (p = 0.07). A shorter duration of fludrocortisone treatment was significantly associated with hypertriglyceridemia (p = 0.009). No significant association was observed between the duration or dose of glucocorticoid therapy, nor the dose of fludrocortisone, and any lipid components (p > 0.05). These findings suggest the importance of screening for clinical signs of insulin resistance and considering the role of mineralocorticoid therapy in the comprehensive metabolic management of these patients.

Keywords: Congenital Adrenal Hyperplasia; Dyslipidemia; Acanthosis Nigricans; Fludrocortisone; Glucocorticoid.

I. INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic disorder, with more than 90% of cases caused by 21-hydroxylase deficiency due to mutations in the *CYP21A2* gene.[1] This condition is characterized by impaired cortisol and aldosterone synthesis, leading to excessive androgen production. Therefore, lifelong glucocorticoid and mineralocorticoid replacement therapy remains the cornerstone of treatment.

Several studies have reported that children with CAH are at increased risk of metabolic disturbances, particularly dyslipidemia. Specifically, these patients tend to exhibit elevated triglycerides, low-density lipoprotein cholesterol (LDL-C), total cholesterol, and reduced high-density lipoprotein cholesterol (HDL-C), which may contribute to an increased risk of long-term cardiovascular complications.[2,3]

Clinical factors and long-term treatment-related factors, including the dosage and duration of glucocorticoid and fludrocortisone therapy, have been suggested to influence lipid abnormalities; however, these associations have not been fully elucidated in previous studies.[4,5] In Vietnam, several studies on congenital adrenal hyperplasia have described clinical characteristics, diagnostic features and genetic mutations in affected children.[6,7]

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However, evidence regarding metabolic complications, particularly dyslipidemia, remains limited.[8] Therefore, this study was conducted to evaluate the association between clinical and therapeutic factors and dyslipidemia in children with CAH at the Vietnam National Children's Hospital, aiming to provide additional evidence to improve management strategies and reduce long-term cardiovascular risks in this population.

II. MATERIALS AND METHODS

1. Subjects

This study was conducted on 73 children diagnosed with CAH who were receiving treatment and follow-up at the Center for Endocrinology, Metabolism, Genetics, and Molecular Therapy, Vietnam National Children's Hospital.

Patient selection criteria

- Patients aged 1 to 17 years old had a confirmed diagnosis of CAH according to the 2018 Endocrine Society Clinical Practice Guideline.[9]

- Had been on treatment for at least 12 months.

- Written informed consent was obtained from parents or legal guardians.

Exclusion criteria

- Patients with concomitant chronic diseases or congenital anomalies affecting lipid metabolism, including congenital heart disease, epilepsy, malignancy, or other relevant chronic conditions, were excluded.

2. Methods

Research methods

Cross-sectional descriptive study

Sample selection and sample size

Convenience sampling method, including all eligible patients during the study period. As congenital adrenal hyperplasia is a rare disease and the study was conducted at a single tertiary center, the number of eligible patients with complete clinical and lipid profile data during the study period was limited. Therefore, the final sample size was determined by the number of available eligible cases rather than by formal sample size estimation. A total of 73 patients were included in the final analysis.

Study location and duration

The study was conducted at the Center for Endocrinology, Metabolism, Genetics and Molecular Therapy, Vietnam National Children's Hospital, from July 2024 to April 2025.

Data collection and study variables

Data were collected through structured interviews, clinical examinations, and retrospective medical record reviews. The following variables were collected:

Demographic variables: age, gender.

- Clinical variables: disease subtype; clinical features suggestive of metabolic disturbances (Cushingoid features, acanthosis nigricans); blood pressure classified according to the 2017 American Academy of Pediatrics guideline,[10] daily glucocorticoid dose, daily fludrocortisone dose at the time of assessment, and duration of glucocorticoid and fludrocortisone therapy. Glucocorticoid doses were converted to hydrocortisone-equivalent doses using the following conversion ratios: 1 mg prednisolone equivalent to 5 mg hydrocortisone, and 1 mg dexamethasone equivalent to 80 mg hydrocortisone.

- Laboratory variables: fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Laboratory parameters were evaluated based on age- and sex-specific reference thresholds, including:

- Dyslipidemia: total cholesterol ≥ 200 mg/dL (5,17 mmol/L), LDL-C ≥ 130 mg/dL (3,36 mmol/L), triglyceride ≥ 100 mg/dL (1,13 mmol/L) (0-9 years old) or ≥ 130 mg/dL (1,469 mmol/L) (10-19 years old), HDL-C < 40 mg/dL (1,03 mmol/L).

- Fasting glucose: normal < 5.6 mmol/L; impaired fasting glucose 5.6-6.9 mmol/L.

Statistical analysis

Data were entered and analyzed using SPSS version 20.0. Continuous variables were expressed as mean ± standard deviation for normally distributed data or median (min-max) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the independent t-test or one-way ANOVA for normally distributed variables, and the Mann-Whitney U test or Kruskal-Wallis test for non-normally distributed variables. The Chi-square test or Fisher's exact test was used for categorical variables, as appropriate. A p-value < 0.05 was considered statistically significant. As the sample size was limited to 73 patients and the number of events was small in several lipid abnormality subgroups, particularly LDL-C abnormality, the study may have been underpowered to detect statistically significant associations in these subgroup analyses. Therefore, multivariable regression analysis was not performed for these outcomes to avoid overfitting and unstable estimates. The findings from subgroup analyses should be interpreted cautiously.

3. Research ethics

This study was approved by the Ethics Committee of Vietnam National Children's Hospital (Decision No. 2685/BVNTW-HĐĐĐ).

III. RESULTS

Table 1. General characteristics of the study population

Characteristics		Salt-wasting (n = 56)	Simple virilizing (n = 17)	Total (n = 73)
Epidemiological variables	n (%)	56 (76.7)	17 (23.3)	73
	Male, n (%)	30 (53.6)	9 (52.9)	39 (53.4)
	Age (years)	10.9 (2.7 - 15.9)	11.1 (3.4 - 15.8)	10.9 (2.7 - 15.9)
Clinical characteristics	Cushingoid features, n (%)	9 (16.1)	3 (17.6)	12 (16.4)
	Acanthosis nigricans, n (%)	10 (17.9)	5 (29.4)	15 (20.5)
	Elevated blood pressure and hypertension, n/N (%)	3 (8.3)/36	2 (14.3)/14	5 (10)/50
Laboratory parameters	Fasting blood glucose (mmol/L)	4.6 (3.6 - 6.3)	4.5 (3.9 - 6.5)	4.6 (3.6 - 6.5)

A total of 73 children with congenital adrenal hyperplasia were included in the study, including 56 patients with the salt-wasting form (76.7%) and 17 patients with the simple virilizing form (23.3%). The median age of the study population was 10.9 years old (2.7-15.9), and 53.4% were male. Notable clinical characteristics included Cushingoid features in 16.4% of patients, acanthosis nigricans in 20.5%, and elevated blood pressure or hypertension in 10% of cases.

Table 2. Association between selected clinical features and dyslipidemia

Lipid abnormalities	Acanthosis nigricans		*p**	Cushingoid features		*p**
	Yes (n = 6)	No (n = 25)		Yes (n = 4)	No (n = 27)	
Low HDL - C, n (%)	0	5 (20)	*0.55*	0	5 (18.5)	*1.0*
High LDL - C, n (%)	3 (50)	1 (4)	***0.016***	2 (50)	2 (7.4)	***0.07***
Lipid abnormalities	**Acanthosis nigricans**		***p****	**Cushingoid features**		p*
	Yes (n = 15)	**No (n = 58)**		**Yes (n = 12)**	**No (n = 51)**	
High total cholesterol, n (%)	3 (20)	8 (13.8)	*0.69*	4 (33.3)	7 (11.5)	*0.075*
High triglyceride, n (%)	7 (46.7)	24 (41.4)	*0.71*	7 (58.3)	24 (39.3)	*0.22*

** Fisher's exact test*

NA: Not applicable

Acanthosis nigricans was significantly associated with high LDL-C (50.0% vs. 4.0%; p = 0.016). Cushingoid features showed a similar trend toward an association with high LDL-C (50.0% vs. 7.4%), although this did not reach statistical significance (p = 0.07). There was no statistically significant associations observed between these clinical features and low HDL-C, high total cholesterol, or high triglyceride (p > 0.05).

Table 3. Association between treatment duration and dyslipidemia in children with congenital adrenal hyperplasia

Associated factors	Lipid index	Normal	Abnormal	*p**
Duration of glucocorticoid therapy (years)	HDL - C (n = 31)	10.9 (4.1 - 15.7)	10.3 (2.7 -13.5)	*0.51*
	LDL - C (n = 31)	10.9 (2.7 - 15.7)	9.5 (4.2 - 13.7)	0.55
	Total Cholesterol (n = 73)	10.4 (1.7 - 15.7)	10.7 (4.2 - 14.7)	*0.52*

Associated factors	Lipid index	Normal	Abnormal	p*
Duration of glucocorticoid therapy (years)	Triglyceride (n = 73)	10.7 (3.4 - 15.4)	8.3 (1.7 - 15.7)	*0.08*
Duration of fludrocortisone therapy (years)**	HDL - C (n = 31)	12.5 (4.2 - 15.7)	10.3 (2.7 - 13.5)	*0.29*
	LDL - C (n = 31)	11.9 (2.7 - 15.7)	11.5 (10.3 - 12.7)	*0.88*
	Total Cholesterol (n = 73)	10.7 (1.7 - 15.7)	11.8 (4.8 - 14.7)	0.55
	Triglyceride (n = 73)	12.3 (5.2 - 15.4)	9.0 (1.7 - 15.7)	***0.009***
Daily glucocorticoid-equivalent dose (mg/m^2/day)	HDL - C (n = 31)	17.7 (13.8 - 24.5)	17.6 (10.8 - 22.7)	*0.707*
	LDL - C (n = 31)	17.6 (10.8 -24.5)	18.2 (13.8 - 20.9)	*0.860*
	Total Cholesterol (n = 73)	17.6 (10.8 - 24.5)	18.2 (13.8 - 20.9)	*0.432*
	Triglyceride (n = 73)	17.6 (11.1 - 24.5)	18.6 (10.8 - 23.8)	0.867
Daily fludrocortisone dose (mg/day)**	HDL - C (n = 31)	0.033 (0 - 0.1)	0.033 (0 - 0.1)	*0.277*
	LDL - C (n = 31)	0.033 (0 - 0.1)	0.025 (0 - 0.1)	*0.66*
	Total Cholesterol (n = 73)	0.033 (0 - 0.1)	0.025 (0-0.1)	*0.797*
	Triglyceride (n = 73)	0.033 (0 - 0.1)	0.033 (0-0.1)	*0.599*

**Mann-Whitney Test*

*** Analyses related to fludrocortisone were performed only in patients with the salt-wasting form, as fludrocortisone is indicated exclusively for this subtype*

No significant difference in glucocorticoid treatment duration was observed between patients with and without dyslipidemia ($p > 0.05$). Among patients receiving fludrocortisone, treatment duration was significantly shorter in those with hypertriglyceridemia (9.0 vs. 12.3 years; $p = 0.009$), but not in other lipid abnormalities ($p > 0.05$). No significant difference existed in daily glucocorticoid-equivalent dose or fludrocortisone dose between groups ($p > 0.05$).

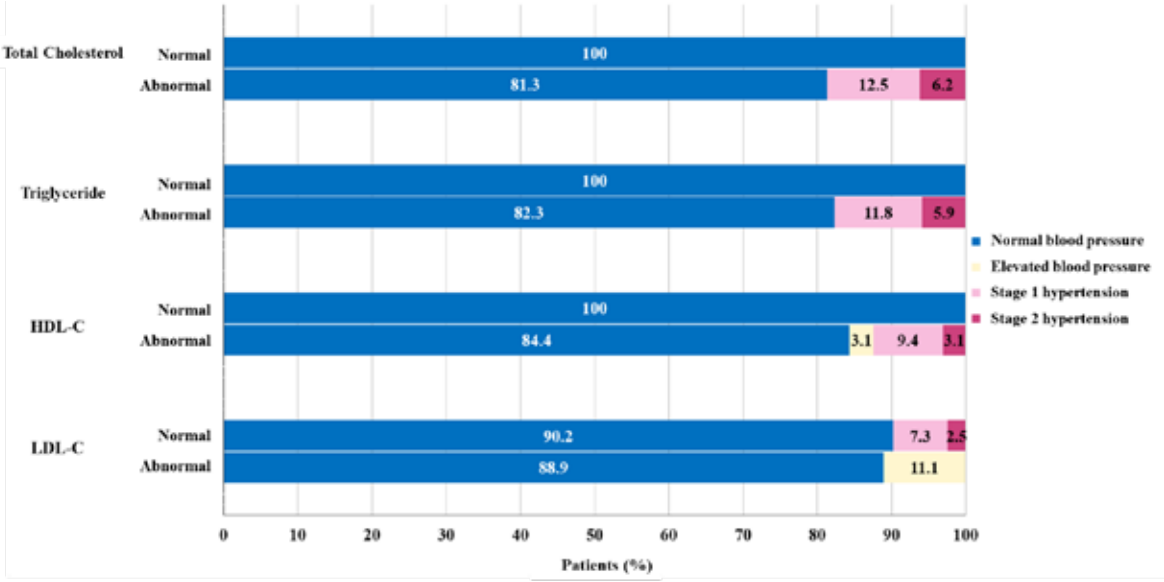

Figure 1. Distribution of blood pressure categories across lipid abnormality groups

In patients with LDL-C and triglyceride abnormalities, all had normal blood pressure (100%). In patients with total cholesterol abnormality, 11.1% had elevated blood pressure; however, this difference was not statistically significant compared to those without abnormality.

Additionally, the prevalence of impaired fasting glucose was higher in patients with hypertriglyceridemia (16.1% vs. 7.1%), although the difference was not statistically significant ($p = 0.27$). Fasting glucose levels were within the normal range in other lipid abnormality groups.

IV. DISCUSSION

This study is among the few in Vietnam to investigate the association between clinical and treatment-related factors and dyslipidemia in children with CAH.

Our findings demonstrated that acanthosis nigricans was significantly associated with LDL-C abnormality ($p = 0.016$), suggesting a potential role of insulin resistance in the pathogenesis of dyslipidemia. In addition, the prevalence of impaired fasting glucose was higher in patients with hypertriglyceridemia (16.1% vs. 7.1%), although the difference was not statistically significant. These findings are consistent with those reported by Improda et al. (2019), who observed elevated HOMA-IR levels, a marker of insulin resistance, in children with CAH.[5] Similarly, Amr et al. (2014) reported that the prevalence of impaired fasting glucose in children with CAH could reach up to 34%, further highlighting the metabolic risk in this population.[11]

Cushingoid features showed a trend toward an association with LDL-C abnormality ($p = 0.07$), although statistical significance was not achieved. This clinical feature may reflect the cumulative effects of glucocorticoid exposure. Borges et al. (2021) reported an association between hydrocortisone-equivalent dose and lipid abnormalities.[12] However, in our study, no significant association was found between daily glucocorticoid-equivalent dose and lipid parameters. Furthermore, Borges et al. also demonstrated that treatment duration was not associated with TC/HDL-C and LDL-C/

HDL-C ratios in multivariable analysis, which is consistent with our findings.[12]

Regarding fludrocortisone therapy, a shorter treatment duration was significantly associated with hypertriglyceridemia (p = 0.009), whereas no significant association was observed with fludrocortisone dose. Given the cross-sectional design and relatively small sample size, these findings should be interpreted with caution. Nevertheless, Torky et al. (2021) reported that mineralocorticoid dose was an independent risk factor for elevated LDL-C in adults (OR = 1.1241; 95% CI: 1.0339-1.2221; p = 0.0061) and reduced HDL-C in children (OR = 1.0069; 95% CI: 1.0025-1.0113; p = 0.0021), suggesting a potential role of mineralocorticoid therapy in lipid metabolism.[13]

Other factors, including blood pressure and impaired fasting glucose, were not significantly associated with dyslipidemia in this study. However, given the limited sample size, these findings require further validation in larger studies.

This study has several limitations. First, the cross-sectional design precludes causal inference. In addition, the relatively small sample size may limit statistical power. As a result, several subgroup analyses, especially those of specific lipid abnormalities such as LDL-C, may have been underpowered. Therefore, these subgroup findings should be interpreted with caution and require confirmation in larger multicenter studies. Furthermore, the absence of a control group restricts comparative interpretation. Some important metabolic variables were not fully assessed in the present analysis, including waist circumference, fasting insulin, and HOMA-IR, because these measurements were not routinely performed in all patients. This may have limited our ability to comprehensively evaluate the relationship between dyslipidemia, adiposity, central obesity, and insulin resistance. Despite these limitations, this study provides one of the first systematic evaluations in Vietnam of the impact of clinical and treatment-related factors on dyslipidemia in children with CAH, contributing valuable real-world data to support clinical monitoring and management in this population.

V. CONCLUSION

Our study demonstrated a statistically significant difference in the prevalence of high LDL-C between patients with and without acanthosis nigricans (p = 0.016). In addition, the duration of fludrocortisone therapy was shorter in patients with hypertriglyceridemia compared to those without (p = 0.009). These findings suggest that clinical indicators of insulin resistance and optimization of mineralocorticoid therapy may play important roles in the development of dyslipidemia in children with congenital adrenal hyperplasia.

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