Prevalence of nephrocalcinosis in children with congenital adrenal hyperplasia

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Background: We aimed to investigate the prevalence of nephrocalcinosis (NC) among children with diagnosed congenital adrenal hyperplasia (CAH). Our findings would be helpful for earlier diagnosis, management, and prevention of NC-related complications.

Materials and Methods: In this cross-sectional study, children with CAH, aged <18 years old who were regularly referred for follow-up, were included. The information of the patients was extracted from their medical files, and they underwent renal ultrasonography for evaluation of the presence of NC. Results: From 120 studied patients with CAH, four patients (3.3%) had NC. The prevalence of NC was higher in males than females (P = 0.05). Mean age and age of CAH diagnosis had a trend to be lower in CAH patients with NC than those without. Regression analysis indicated significant association between NC and sex (P = 0.027, r = 2.24). Conclusion: The results of this study indicated a 3.3% prevalence rate of NC for children with CAH. NC had a trend to be more prevalent in male children with CAH. Though it was not significantly different but given that the mean age and age at diagnosis of CAH in children with CAH and NC was lower that CAH patients without NC, it is suggested that in patients with CAH and NC other factors such as genetic background or unknown disease related factors are associated with hypercalcemia and NC.

Key words: Congenital adrenal hyperplasia, nephrocalcinosis, prevalence

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by cortisol coding genes dysfunction and enzymatic defects in the synthesis of glucocorticoid hormones.[1-3] The prevalence of CAH is reported to be 1 in 15,000.[1] The most common form of CAH, the classic type, is 21-hydroxylase deficiency, which accounts for 90%-95% of its cases. The classic CAH results from mutations or deletions of CYP21A gene.[1-3]

Other types of CAH are due to 17α-hydroxylase, 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase, and cytochrome P450 oxidoreductase deficiency.[1-3]

Clinical manifestations of classic CAH are virilization, salt wasting (presented with dehydration and hypotension in the first stage and it could be life-threatening), ambiguous genitalia, premature pubarche, accelerated growth velocity, and skeletal maturation which result in short stature in adulthood, hirsutism, acne, anovulation, and menstrual irregularities. Some cases are asymptomatic. The nonclassic forms of CAH are...
present by sexual ambiguity, arterial hypertension, and craniofacial malformations. CAH treatment is lifelong hormone replacement therapy which is essential for developing normal growth and puberty process in this group of children. The patients should follow-up regularly for both management and monitoring of the growth process and CAH-related complications.\textsuperscript{[4,5]}

Although steroid replacement therapy in children with CAH improves the normal development of the patients and prevents adrenal crises, both the CAH and its treatment could have lifelong impacts on their health and quality of life.\textsuperscript{[7]}

Some CAH-related common complications are obesity, hypertension, metabolic syndrome, and cardiovascular complications.\textsuperscript{[7]} Some others such as hypercalcemia and nephrocalcinosis (NC) are rare but well recognized due to that they are almost not recognized earlier and they could result in other complications such as growth failure or acute renal failure.\textsuperscript{[8]}

As mentioned, most of the NC cases remained unrecognized and they were detected after presentations of NC-related outcomes. Hence, NC considered an important comorbidity with CAH, which should evaluate during follow-up period of the patients.

A few studies have reported the rate of NC in CAH patients and emphasized on its importance in this group of patients.\textsuperscript{[9]} However, there are not many studies in this field. In addition considering that the rates of NC and its etiologies are different in different ethnic, geographical, or socioeconomic conditions, it would be more practical to determine the rate of NC in both healthy and children with certain diseases in order to plan more comprehensive management and follow-up plan for children with certain diseases such as CAH.\textsuperscript{[10,11]}

Thus, we aimed to investigate the prevalence of NC among children with diagnosed CAH referred to the referral pediatric hospital in Isfahan, Iran. However, understanding the rate of NC in this group of patients would help the pediatric endocrinologist for earlier diagnosis and management of the problem and prevention of NC-related complications.

**MATERIALS AND METHODS**

This study was designed as a cross-sectional study in Isfahan, Iran. The study was conducted from March 2020 to September 2020.

The protocol of the study was approved by the Regional Ethics Committee of Isfahan University of Medical Sciences with a research project number of 398632 and ethics code of IR.MUI.MED.REC.1398.701.

In this study, children with a confirmed diagnosis of CAH (based on clinical, biochemical, or genetic findings), aged <18 years old who were regularly referred to Imam Hossein Children’s Hospital, affiliated to Isfahan University of Medical Sciences, were included. Those with irregular follow-ups, inappropriate cooperation, and cases of idiopathic hypercalcinosis were excluded from the study.

The protocol of the study was described for the patients and/or their parents in detail and a written consent form was completed by those who accepted to participate in the study.

The information of the patients was extracted from their medical files, including age, sex, duration of the disease and treatment, and results of biochemical measurements. The patients underwent renal ultrasonography by an expert pediatric radiologist (MR), and the presence of NC was reported.

Ultrasonography was performed by VOLUSON E8 (GE Medical Systems, Kretz Ultrasound, USA) ultrasound instrument using linear and curved transducers. Renal ultrasonography of all patients was performed by an expert radiologist M.R in Imam Hossein Children’s Hospital.

Characteristics of patients with and without NC were compared.

**Statistical analysis**

Data were analyzed using SPSS version 24 software (IBM SPSS/PC Inc., Chicago). Continuous and categorical variables were presented by mean (standard deviation) and n (%). Characteristics of patients with and without NC were compared using Chi-square and student t-test. \( P < 0.05 \) considered statistically significant.

**RESULTS**

In this study, from 120 patients with a confirmed diagnosis of CAH who were followed up in the hospital, four patients (four male) had NC. The prevalence of NC was 3.3% (0.09–0.03 confidence interval [CI] 95%) in our studied population. The mean age of the studied population was 9.7 (4.76) with the male-to-female ratio of 1 (60/60).

Characteristics of patients with and without NC are presented in Table 1. The prevalence of NC was higher in males than females \( (P = 0.05) \).

Mean age and age of CAH diagnosis had a trend to be lower in CAH patients with NC than those without.
Regression analysis indicated significant association between NC and sex ($P = 0.027$, $r = 2.24$).

**DISCUSSION**

In this study, we evaluated the prevalence of NC in children with CAH. We found that 3.3% of the patients had NC and it was more prevalent among male patients. Although it was not statistically significant, it seems that children with NC had lower mean age and lower age at diagnosis.

There are few studies regarding the prevalence of NC in children. Based on available data, it is suggested that the prevalence of NC in the general pediatric population is 5%. In a study in Saudi Arabia, the causes of NC among pediatric population were investigated. Based on their results, the most common causes of NC were hereditary tubulopathy and hyperoxaluria. They reported that 3% of the cases with NC had CAH, which is considered an uncommon cause for NC.

As mentioned, though NC is a rare complication of CAH, considering its related important impacts on children growth and renal function, it is considered an important issue in the management of this group of patients.

In the literature review, we found few studies which investigated the possible association between CAH and NC. Previous studies were mainly case reports and studies which evaluated a large sample size of patients were few.

Yang, et al. demonstrated that congenital adrenal disorders such as hyperaldosteronism could effect on renal function of the patients. They also indicated that NC is one of the rare complications of the disorders which commonly presented as medullary NC (95%) and only 5% of the NC cases are cortical NC.

Shey et al. reported a case of primary hyperaldosteronism with severe recurrent NC. Based on their investigation, the two most trigger factors for NC were hypocitraturia and hypercalciuria. They concluded that though NC is a rare complication of hyperaldosteronism which has not been evaluated well, and there are few epidemiological studies in this field.

Mittal et al., in 2015, for the first time reported two cases of CAH with medullary NC. They concluded that both primary aldosteronism and chronic hyperaldosteronism secondary to any cause could be a potential risk factor for NC.

Aswani, et al. in 2015 also reported a case of CAH (male) with 11 beta-hydroxylase deficiency presented with renal cysts and NC. Similarly, Abdulla et al. reported a male with CAH due to 11 beta-hydroxylase deficiency presented with renal cysts and NC.

They suggested that NC in this group of patients is a secondary outcome of hypokalemia-induced interstitial nephritis.

Recently, Schoelwer et al. in the USA have investigated the rate of hypercalcemia, hypercalciuria, and NC among CAH patients who were diagnosed before the age of 2 years. They studied 40 patients. From these patients, 33 (84%) had hypercalcemia, 6 (15%) had hypercalciuria, and 3 (6%) had NC. Most of their studied patients were <6 years old.

They concluded that one of the most important risk factors of NC is hypercalciuria. They indicated that though hypercalciuria is a common finding in children with classic CAH, it is not evaluated during the routine follow-up period of the patients. They recommended to include Ca measurements in children with CAH and plan studied to determine the etiology of hypercalciuria in these patients.

In this study, we reported a 3.3% rate for NC. Considering that the mean age of our studied population was higher than that reported in Schoelwer et al.’s study and the trend of higher rate of NC in patients with lower age and lower age at diagnosis of CAH, the difference could be explained. Schoelwer et al. studied only children with CAH who were diagnosed before 2 years of age.

Almost of the reported cases of CAH with NC in previous studies were male. In our study, all of the patients with CAH...
and NC were male, and there was a significant association between male gender and NC in this group of patients.

The main limitation of our study was its retrospective design. It seems that designing prospective studies in this field would be more helpful for determining the risk factors of NC in CAH. The strength of this study was that there was not any study in this field among the Iranian population. The available evidences in this field were also few.

**CONCLUSION**

The results of this study indicated a 3.3% prevalence rate of NC for children with CAH which was similar to that reported by other studies. NC had a trend to be more prevalent in male children with CAH. Although it was not significantly different, given that the mean age and age at diagnosis of CAH in children with CAH and NC were lower than CAH patients without NC, it is suggested that in patients with CAH and NC, other factors such as genetic background or unknown disease-related factors are associated with hypercalcemia and NC. More prospective studies are needed to determine the possible risk factors related to NC in children with CAH.

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**Conflicts of interest**

There are no conflicts of interest.

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