

Case report

Co-existence of non-classical congenital adrenal hyperplasia and Bartter syndrome complicated with central precocious puberty: A rare presentationMilind Ballal¹, Akshatha U. Shetty¹, Supreetha Shetty²¹Department of Paediatrics, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India²Consultant Paediatric Endocrinologist, AJ Hospital and Research Centre, Mangalore, Karnataka, India

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Corresponding author: **Milind Ballal**. Email: milindballal09@gmail.com**ABSTRACT**

Congenital adrenal hyperplasia is an autosomal recessive disease marked by lack of enzymes required to produce specific hormones. About 90-95% of CAH are caused by steroid 21-hydroxylase deficiency and are the result of mutations in the *CYP21A2* gene. Bartter syndrome is a rare autosomal recessive disorder characterized by hyperreninemia, metabolic alkalosis, hypokalaemia, and hypochloremia by activation of the RAS. The underlying renal abnormality results in electrolyte and acid-base imbalance abnormalities. We present a rare case of NCCAH coexisting with Bartter syndrome. A 5 years and 7 months old male was diagnosed with NCCAH at 20 days of life presented with fever and cold for one month, as well as recurrent UTIs for two weeks. General physical examination revealed carpopedal spasm, pubic hairs (+) with penile length (8.5 cm). Investigation revealed kaliuresis, hypercalciuria, metabolic alkalosis, hypokalaemia, and hypochloremia. X-ray of the left wrist revealed bone age as 9 years and genetic analysis was recommended. NCCAH with coexisting BS complicated with central precocious puberty was diagnosed. Symptomatic treatment was administered, and long-term steroid replacement advised. Congenital adrenal hyperplasia and Bartter syndrome is difficult to treat, and there is currently no complete cure. Close monitoring and prompt electrolyte replacement with symptomatic treatment are recommended.

Keywords: Bartter syndrome; non-classical congenital adrenal hyperplasia; central precocious puberty.**INTRODUCTION**

Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder condition defined by enzyme deficiency, which is one of the five steps necessary for the adrenal cortex to synthesise cortisol from cholesterol by activation of the renin angiotensin system (1). About 90–95% of CAH cases are caused by 21-OHD enzyme deficiency and are the result of mutations in the *CYP21A2* gene, whereas HSD3B2 enzyme deficiency is uncommon (2). In literature, there are primarily three clinical phenotypes that have been described: classical salt-losing, classical non-salt-losing, and non-classical (1). Bartter syndrome (BS) is a rare hereditary renal tubular condition that affects roughly 1 in 1,000,000 people which is marked by a defect in salt reabsorption in the thick ascending limb (TAL) of the loop of Henle, results in electrolyte and acid-base imbalance abnormalities (3). Metabolic alkalosis, hypokalemia, and hypochloremia are caused by increased urine sodium, chloride, and potassium losses as a result of the underlying renal dysfunction. Based on genetic mutation Bartter syndrome is classified into five types which have different clinical presentations (4). There are two main subtypes of precocious puberty: central precocious puberty (GnRH dependent) and peripheral precocious puberty (GnRH independent). We here presented this unusual case of Non-classical CAH (NCCAH) along with Bartter Syndrome complicated with central precocious puberty in a paediatric patient.

Case report

A 20-day old male child with no significant antenatal and perinatal history born to a 2nd degree consanguineously married couple presented with c/o poor feeding and lethargy from 2 days. His investigations revealed hyponatraemia, hyperkalaemia. Further investigations showed an elevated 17-hydroxyprogesterone of >2000 ng/dl. For which the child was diagnosed to have congenital adrenal hyperplasia and was commenced on Hydrocortisone and Fludrocortisone, but the patient attendants were non-compliant with the medication and discontinued it three years ago without consulting. At 5 years 7 months of age, he was brought by his parents with complaints of fever and cold for one month and repeated urinary tract infections (UTIs) for the past two weeks.

Physical examinations revealed bilateral carpopedal spasm, pallor, hypopigmented lips (Fig.1), stretched penile length was 8.5 cm and pubic hair distribution matched with Tanner stage 3, while systemic examination was unremarkable (Fig.2). Patient was admitted for further evaluation, a routine lab investigation revealed kaliuresis, hypercalciuria, metabolic alkalosis, hypokalemia, and hypochloremia.



Fig.1: Hypopigmented lips



Fig. 2 : External genitalia showing features of precocious puberty

He was started on sodium chloride supplement, fludrocortisone, and hydrocortisone (10 mg/m² /day). He was gradually weaned off of fludrocortisone due to the persistence of hypokalaemic alkalosis, but he continued to be hypokalaemic, with plasma concentration of potassium constantly remaining under 3 mmol/l (Table 1.). 2 mmol/kg/day of potassium supplements were started; however, the potassium levels did not significantly improve. An underlying tubulopathy was suggested because of the unique electrolyte constellation with hypokalaemic,

hypochloraemic metabolic alkalosis in the context of an underlying mineralocorticoid deficit. After evaluation and examination, Non-Classical Congenital Adrenal Hypoplasia with coexisting Bartter syndrome was suspected. In addition, genetic screening was planned for further evaluation, but patient attendants declined due to financial constraints.

Since the child had pubic hairs and a stretched penile length (8.5cm), an X-ray of the left wrist was performed to rule out precocious puberty (Fig.3). The bone age was confirmed to be 9 years. The baseline levels of FSH, LH, and total testosterone indicated that LH and testosterone were in the pubertal range. GnRH stimulation tests were performed which inferred central precocious puberty. Baseline hormonal levels and GnRH stimulation test results are mentioned in Table 2. A plain MRI was performed to rule out a CNS tumour causing central precocious puberty. As a consequence of congenital adrenal hyperplasia, his diagnosis was central precocious puberty on peripheral precocious puberty. So the child was started on GnRH analogues.

Table 1: Serial lab investigations

Electrolytes (in mmol/l)	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7
Na	144	143	143	147	143	144	140
K	2.7	2.2	3	2.5	2.5	3.2	4.8
Cl	77	88	97	95	87	94	102

Table 2: Baseline hormone levels and GnRH stimulation test

Variables	Luteinizing Hormone (mIU/ml)	Follicle Stimulating Hormone (mIU/ml)	Total Testosterone (mg/dl)
Baseline	0.30	1.09	81
2 hours post Inj.Leuprolide	5.96	3.46	-
24 hours post Inj. Leuprolide	-	-	73



Fig. 3 : X-ray of left hand for bone age estimation showing bone age of 9 years

The general condition of the child improved and the electrolytes levels were within normal ranges. The child was sent on hydrocortisone, fludrocortisone, indomethacin, GnRH analogues (to be taken once in every 4 weeks). Currently the child is on regular follow up and has responded well to the treatment.

DISCUSSION

Several genetic conditions that affect the adrenal glands can result in congenital adrenal hyperplasia. Although CAH is rare, the most common form is 21-OHD, an autosomal-recessive disease of adrenal steroidogenesis caused by *CYP21A2* mutations (1). There are two distinct subtypes of 21-OHD CAH: the severe classic CAH (CCAH) and the mild Non-Classical CAH (2). Deficiencies in the hormones cortisol, aldosterone and adrenaline—all crucial components of numerous homeostatic pathways—cause the potentially fatal syndrome known as classic 21-OHD CAH, and compensatory responses results in overproduction of adrenal androgens. (5). The non-classical variant is connected to *CYP21A2* mutations that preserves about 20–55% of the enzyme function. This kind is quite prevalent and has no symptoms sometimes (6). In CAH, peripheral precocious puberty (PPP) is frequently caused by increased androgen production. The PPP in CAH is frequently caused by increased androgen production. The hypothalamic-pituitary axis may be stimulated by prolonged hyperandrogenemia, resulting in central precocious puberty (CPP), which affects stature by increasing bone age (7). Gonadotropin levels are reduced by GnRH agonists' medication, secondary sexual characteristics are stabilised, and the rate of linear development and BA maturation is slowed (8).

In 1962, Bartter et al. identified two African Americans with a novel disease entity that is now known as Bartter syndrome. The Na-K-2Cl cotransporter (NKCC2), apical K channel (ROMK), or basolateral chloride channel (CLCNKB) are the three principal transporters taking part in sodium chloride reabsorption in the thick ascending limb of the loop of Henle or distal convoluted tubule that are pathologically the primary defects. When these channels are defective, the thick ascending loop of Henle fails to absorb sodium, potassium, chloride and calcium.

Final results of these defects are hypokalemia, reduced NaCl transport, reduction in water reabsorption in collecting ducts hyposthenuria and hypovolaemia which activates the renin-aldosterone axis, resulting in hyperaldosteronism, which results in K⁺ wasting (hypokalemia) and metabolic alkalosis. When K⁺ channels open and close, which is regulated by intracellular calcium and cell ATPase, hypercalciuria is the outcome. Volume loss is the reason why blood pressure remains normal despite elevated renin-aldosterone levels. Fluid deficiency and electrolyte imbalance must be corrected to treat Bartter Syndrome

(3,9). Indomethacin is a regularly used prostaglandin synthetase inhibitor. Rofecoxib, a brand-new cyclooxygenase-2 inhibitor, can be used instead in case of failed indomethacin therapy (3). As far as the primary disease and related co-morbidities are concerned, the long-term prognosis of Bartter Syndrome should always be cautious. Nearly all Bartter Syndrome patients will eventually develop persistent hypercalciuria and medullary nephrocalcinosis (10).

There is not much literature on the rare combination of congenital adrenal hyperplasia and Bartter syndrome, therefore this study fills in the gaps with information that can help us better understand the condition and develop better diagnostic and therapeutic approaches.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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