Central Precocious Puberty as a Sign of Congenital Adrenal Hyperplasia: Case Presentations

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Abstract: Central precocious puberty results from the premature activation of the hypothalamic-pituitary-gonadal axis. Rarely congenital adrenal hyperplasia and/or its inappropriate treatment can be a peripheral cause of CPP. There are very few case reports of this etiology. Chronic mildly to moderately elevated adrenal androgens or intermittent hyperandrogenemia in congenital adrenal hyperplasia may trigger the precocious activation of the hypothalamic-pituitary axis, leading to CPP. In the current work, we describe 6 cases of late diagnosis of congenital adrenal hyperplasia associated with central precocious puberty. Central precocious puberty seems to be a complication of congenital adrenal hyperplasia, particularly in countries where a routine neonatal screening program for this condition is lacking. It is unclear whether these patients could avoid central precocious puberty development if the congenital adrenal hyperplasia was diagnosed in the neonatal period and appropriately treated. The current work underlines the need for congenital adrenal hyperplasia neonatal screening implementation and further investigation of the association of these two endocrine disorders.

Keywords: Precocious puberty, congenital adrenal hyperplasia.

INTRODUCTION

Central precocious puberty (CPP) results from the early activation of the hypothalamic-pituitary-axis (HPA). It imitates physiological pubertal development, although at an inappropriate chronological age (before 8 years of age in girls, and 9 years of age in boys) [1]. It is known that CPP is caused by lesions of the central nervous system (CNS), genetic mutations, or idiopathic reasons. Rarely congenital adrenal hyperplasia (CAH) can be a peripheral cause of CPP. Very exceptional case reports of this etiology are described in the literature [2, 3]. CAH is an autosomal-recessive disorder caused by enzymatic defects in the corticosteroid synthesis pathway, characterized by deficient production of end steroid hormones: cortisol and/or aldosterone. Decreased cortisol concentration leads to a compensatory increase of adrenocorticotropic hormone secretion (ACTH) and hypertrophy of the adrenal cortex, consequently resulting in androgens excess production [4-6]. Elevated adrenal androgens or intermittent hyperandrogenemia may trigger the activation of the HPA, leading to CPP [7-9]. In several countries, CAH is diagnosed early after birth due to neonatal screening programs.

In the current work, we recruited 5 patients with CAH, who were followed by pediatric endocrinologists. Data were abstracted from the patients' medical records, including age, sex, clinical data, and relevant biochemical, hormonal, and radiological investigations. The diagnosis of CAH and CPP was established according to the standard criteria based on clinical, laboratory, and endocrinological evaluation and performed stimulation tests [10].

CASE PRESENTATION

Case 1

A 2.5 years old boy was admitted to the outpatient clinic of Endocrinology with complaints of pubic hair growth, the darkness of the scrotum, and growth acceleration. Medical and family history was unremarkable. The signs of sexual development were revealed by parents last year. At the admission, bone age was accelerated from the chronological age and corresponded to 8 years of age—sexual development based on secondary sexual signs corresponded to the Tanner III stage. The height standard deviation (SD) was +2.8. He started treatment with hydrocortisone and fludrocortisone, which resulted in good biochemical, hormonal, and clinical control of a child. Then after, at the age of 5 years, with the reasonable compliance to the administered treatment, the growth and bone age acceleration continued, and the patient underwent the stimulation test by GnRH, which revealed CPP. He was administered GnRH long-acting analogue-depot in once a month. The next two-three years showed no longer acceleration of bone age and height velocity. The child is 7 years old now and taking hydrocortisone, fludrocortisone, and GnRH long-acting analogue-depot.

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Case 2

A 4 years old boy was referred to the pediatric endocrinologist with complaints of growth acceleration and pubic hair growth. Height SD was +4.16, and bone age corresponded to 13-14 years. Hydrocortisone and fludrocortisone were prescribed, respectively. At the age of 5.5 years, a stimulation test with GnRH was performed, and CPP was diagnosed. He started with the treatment of GnRH long-acting analogue-depot intramuscular monthly injections. The child is 7.5 years old now with no progression of sexual signs' development.

Case 3

The pediatric endocrinologist examined a 6 months old boy due to weight loss, vomiting, pubic hair growth, and darkness of scrotum. He was diagnosed with CAH and multicystic kidney. He started the treatment with hydrocortisone and fludrocortisone. At the age of 4 years, growth, bone age acceleration, and pubic hair growth were revealed, and CPP was diagnosed based on the GnRH stimulation test results. Now the child is 4 years old and receives GnRH long-acting analogue-depot once monthly added to hydrocortisone and fludrocortisone.

Case 4 and 5 are Two Brothers

The senior brother was diagnosed with CAH at the age of 4 years old due to accelerated growth and pubic hair. At the routine preventive examination of his sister and brother, the CAH clinical features were found in the brother of 2 years of age, and CAH was diagnosed based on analyses and genetic mutation. CPP in case 4 and case 5 was diagnosed at the age of 6 and 2.5 years, respectively. These two cases were published as a family case of association of CAH and CPP [11].

DISCUSSION

CAH rarely can present with GnRH-dependent precocious puberty. The mechanism is due to chronically increased levels of androgen precursors causing early activation of the HPA. In all presented cases, the diagnosis of CAH and treatment were delayed. The progression of bone maturation in these patients can be explained with late diagnosis of CAH, and then after with the CPP progression, despite the appropriate treatment and reasonable compliance of patients. Accelerated bone age at the diagnosis of CAH leads to poorer final height prognosis in these patients. Considering the impact of sex steroids' excess on behavioral and brain developmental processes, further investigations are needed later to evaluate these children's peculiarities.

Since there is no neonatal screening program for CAH in Armenia, the diagnosis of CAH in the majority of cases is late. Current cases demonstrated that CPP can be observed and serve as a sign of late diagnosis and undertreated CAH.

AUTHORS' CONTRIBUTION

R.M. did study concept and design, L.N. Collection, and assembly of the data were done by R.M., L.N. Analysis and interpretation of data: R.M., L.N. Manuscript writing was done by R.M., L.N.

FINANCIAL SUPPORT STATEMENT

This study was conducted without any financial support or sponsor involvement.

CONFLICT OF INTEREST

The author does not declare it.

ETHICAL APPROVAL

Yerevan State Medical University IRB approval N 5/2018.

Informed consent was signed by parents.

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