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FAMILIAL CASE OF CONGENITAL ADRENAL HYPERPLASIA COMPLICATED WITH CENTRAL PRECOCIOUS PUBERTY

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Abstract

Central precocious puberty results from the early activation of the hypothalamic-pituitary-gonadal axis. It imitates physiological pubertal development, although at an inappropriate chronological age. The aetiology of central precocious puberty is often unknown but it's Gonadotropin-releasing hormone dependent. Although central precocious puberty as a rule caused by central nervous system defeat or idiopathic reasons, seldom, congenital adrenal hyperplasia can be a peripheral cause of central precocious puberty. Congenital adrenal hyperplasia is autosomal recessive disorders caused by enzymatic defects in the corticosteroid synthesis pathway that is characterized by deficient production of the steroid hormones cortisol and/or aldosterone. Decreased cortisol concentrations result in loss of the negative feedback inhibition leading to a compensatory increase of adrenocorticotropic secretion and hypertrophy of the adrenal cortex and consequently causing androgen excess. The average raised adrenal androgens or intermittent hyperandrogenemia may trigger the activation of the hypothalamic-pituitary axis leading to central precocious puberty. We experienced the family case of congenital adrenal hyperplasia, complicated by true precocious puberty with early maturation of the hypothalamic-pituitary-gonadal axis in two brothers. In this family, a homozygous I2spl mutation was detected in the two probands during the allele-specific polymerase chain reaction, heterozygous mutation was detected in the mother, and the heterozygous carrier of this mutation was detected in the sister and father. Examination of children in the family with the presence of one patient is mandatory, which will contribute to the timely identification of this pathology in probands. The progression of bone maturation in these patients can be explained with several reasons. On one hand it's connected with late diagnosis of congenital adrenal hyperplasia, on the other hand with low parental compliance related with medicine consumption. The present cases demonstrated that central precocious puberty can be observed in undertreated for congenital adrenal hyperplasia. Central precocious puberty can be a complication of congenital adrenal hyperplasia, especially in countries where a routine neonatal screening program for this condition is missing.

Keywords: *congenital, adrenal hyperplasia, puberty, neonatal screening.*

Introduction

Central precocious puberty results from the early activation of the hypothalamic-pituitary-gonadal axis [*Neely E, Crossen S, 2014*]. It imitates physiological pubertal development, although at an inappropriate chronological age (before 8 years in girls and 9 years in boys) [*Aguirre R, Eugster E, 2018*]. The aetiology of central precocious puberty is often unknown but it's Gonadotropin-releasing hormone-dependent [*Chen M, Eugster E, 2015*]. Although, central precocious puberty as a rule caused by central nervous system defeat or idiopathic reasons, seldom, congenital adrenal hyperplasia can be a peripheral cause of central precocious puberty [*El-Maouche D et al., 2017; Török D, 2019*]. There are very exceptionally case reports of this aetiology.

Congenital adrenal hyperplasia is autosomal recessive disorders caused by enzymatic defects in the corticosteroid synthesis pathway that is characterized by deficient production of the steroid hormones cortisol and/or aldosterone [*Milunsky A, Milunsky J, 2010*; *Hannah-Shmouni F et al., 2017*]. Decreased cortisol concentrations result in loss of the negative

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feedback inhibition leading to a compensatory increase of adrenocorticotropic hormone secretion and hypertrophy of the adrenal cortex [*Merke D, Kabbani M, 2001*] and consequently causing androgen excess [*Balsamo A et al., 2003; Merke D, Bornstein S, 2005; Khalid J et al., 2012*]. The average raised adrenal androgens or intermittent hyperandrogenemia may trigger the activation of the hypothalamic-pituitary axis leading to central precocious puberty. In a number of countries, the diagnosis of congenital adrenal hyperplasia can be identified early, through neonatal screening programs.

We experienced the family case of congenital adrenal hyperplasia, complicated by true precocious puberty with early maturation of the hypothalamic-pituitary-gonadal axis in two brothers.

CASE PRESENTATION

Patient G.A. was admitted to the department of at the age of 4, complaining of acceleration of growth, and sexual development. He had no history of headache, seizures, and visual problems. There was no history of head trauma or surgery or prolonged drug intake. Family history and perinatal history was unremarkable. The signs of precocious puberty appeared at the age of 3; pubic hair growth, growth of penis, the growth spurt was noticed after 3 years old.

The diagnosis "Congenital adrenal hyperplasia, 21 OH deficiency, salt wasting form" was established at the age of 4 based on acceleration of growth (height velocity standard deviation score (SDS)+4.2), symptoms of precocious puberty (appearance of andrenarche, enlargement of penis, testes volume were 2 ml), acceleration of bone age (bone age matched 11 years old at passport age of 4 years and 1 month), high levels of 17 OH-Progesterone (>53 *ng/ml*), adrenocorticotropic hormone (1250 *pg/mL*), plasma renin activity *ng/mL/hour* 3.52. Blood pressure was measured and corresponded <90th centile. The molecular genetic examination of the gene CYP21A2 to common mutations determined mutation I2spl in homozygote form confirming congenital adrenal hyperplasia. A replacement therapy with glucocorticoids in dose 15 *mg/m*^{2} and mineralocorticoids 100 *mcg/daily* was assigned [*Stewart S, 2013*]. During the age of 5 to 6 the kid took the glucocorticoids and mineralocorticoids not regularly, although crises of adrenal insufficiency were not observed.

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

During the admission at the age of 6 the boy's height was 144.8 *cm*, SDS +3.9, height velocity 9.9 *cm/year*, SDS of height velocity +2.2. Sexual development at the moment of examination matched 3 stage by Tanner's classification, testicular volume matched 6-8 *ml*.

At the moment of admission, the patient took therapy with hydrocortisone in dose 12 *mg/m*^{2}. On the x-ray of hand bone the bone age corresponded to 13 years. The study showed elevated levels of 17-OH-progesterone, dehydroepiandrosteone sulfate, testosterone and adrenocorticotropic hormone, the dose of hydrocortisone was increased to 17.5 *mg/m*^{2}, dose of mineralocorticoid remained the same. Based on the progress of bone age, growth speed and basic levels of luteinizing hormone to 3.8 *U/L*, a gonadotropin-releasing hormone stimulation test was done, which showed a pubertal elevation of luteinizing hormone which confirmed central precocious puberty. Magnetic resonance imaging did not show abnormality of the hypothalamus-pituitary region and β-human chorionic gonadotropin levels were at the normal range. Therapy with prolonged analogs of gonadotropin-releasing hormone has been assigned.

The patient has been hospitalized again in the endocrine department after 1 year, at the age of 7. Clinically there was determined deceleration of height velocity up to 4.76 *cm/year* (SDS of height velocity -0.97), 17-OH-progesterone, testosterone and adrenocorticotropic hormone were at the normal range, though the progression of bone age was still in process (matching 14 years old). On the background of therapy with analogs of gonadotropin-releasing hormone the progression of precocious puberty was not determined, the size of testicles remained the same, and during the palpation of testicle structural changes were not detected. Based on the progression of bone age, to exclude testicular adrenal rest tumors [*Ozisik H et al., 2017*], there was done ultrasound examination of scrotal organs. No pathological changes were detected.

The dose of hydrocortisone has been adjusted for the patient, the dose and schedule of analogs of gonadotropin-releasing hormone has remained the same, it was recommended careful dynamic observation.

Due to the fact that congenital dysfunction of

the adrenal cortex is a genetic disease, the patient's brother and sister were examined by an endocrinologist. During the observation the sister of the patient didn't have growth acceleration and precocious puberty, as well as symptoms of virilization were not revealed. However, when examining the patient's brother, an increase in the penile size was found, as well as an acceleration of growth. The boy was admitted to the clinic of endocrinology for examination.

Patient G.N. (2 y.o.) diagnosis congenital adrenal hyperplasia, salt wasting form, was established based on increased height velocity (SDS +3.3), symptoms of precocious puberty (increase in the external genital organs), acceleration of bone age (it matched 7 years old), high levels of 17-OH-progesterone (24 *nmol/l*), adrenocorticotropic hormone (750 *pg/ml*), plasma renin activity 3.7 *ng/mL/hour*, elevated dehydroepiandrosteone sulfate with normal range of testosterone. A replacement therapy with glucocorticoids in dose 12 mg/m^2 and mineralocorticoids 50 *mcg/daily* was assigned. The molecular genetic examination of the gene CYP21A2 to common mutations determined mutation I2spl in homozygote form. The patient took the glucocorticoids and mineralocorticoids regularly; crises of adrenal insufficiency were not observed. On the background of treatment, after 6 months, both clinical and laboratory investigations were done. As by the time there was also noticed presence of central precocious puberty, and gonadotropin-releasing hormone stimulation test was carried out, which showed a pubertal response further confirming central precocious puberty.

The final diagnoses of two cases were gonadotropin-releasing hormone-dependent central precocious puberty possibly due to classic salt wasting congenital adrenal hyperplasia.

Discussion

In this family, a homozygous I2spl mutation was detected in the two probands during the allele-specific polymerase chain reaction [*Concolino P, Costella A, 2018*], heterozygous mutation was detected in the mother, and the heterozygous carrier of this mutation was detected in the sister and father.

Examination of children in the family with the presence of one patient is mandatory, which will contribute to the timely identification of this pathology in probands.

Rarely, congenital adrenal hyperplasia can present with gonadotropin-releasing hormone-dependent precocious puberty in males [*Speiser P, White P, 2003*]. The mechanism is due to chronic increased levels of androgen precursors causing early activation of the hypothalamus. The progression of bone maturation in these patients can be explained with several reasons. On one hand it's connected with late diagnosis of congenital adrenal hyperplasia (4 y.o.), on the other hand with low parental compliance related with medicine consumption.

Since there is no neonatal screening program for congenital adrenal hyperplasia in our country, the diagnosis of patients was late. Regarding our patients, the diagnosis of two brothers also were delayed. The present cases demonstrated that central precocious puberty can be observed in undertreated for congenital adrenal hyperplasia. Central precocious puberty can be a complication of congenital adrenal hyperplasia [*Podgórski R et al., 2018*], especially in countries where a routine neonatal screening program for this condition is missing [*Dulín E, Ezquieta B, 2018*].

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