A rare case of idiopathic central precocious puberty in a 17-month-old girl

Chae-Ho Kim[1], Kyung-Sue Shin[2]

[1]Jeju National University School of Medicine, [2]Department of Pediatrics,

Jeju National University School of Medicine, Jeju, Korea

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Abstract

Central precocious puberty (CPP) is defined as development of secondary sex characteristics in relation with activation of the HPG axis before the age of 8 years in girls and before the age of 9 years in boys. CPP is far less common in children before 3 years of age, particularly in females. Most girls with signs of puberty less than 3 years of age are diagnosed with premature thelarche (PT). Although CPP presenting with early breast development should be differentiated from PT, there is no diagnostic method which would definitely differentiate these two conditions. We present idiopathic CPP before 3 years of age who presented with PT that rapidly progressed to CPP. Up to date, there are no predictive clinical or laboratory tests that can identify the risk of progression to PP at time of onset. Therefore, all girls with PT should be monitored clinically for accelerated pubertal progression. **(J Med Life Sci 2015;12(2):103-106)**

Key Words : Precocious puberty; Premature thelarche; Premature pubarche

INTRODUCTION

Precocious puberty (PP) is defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys[1]. It caused by the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, which is known as true or central precocious puberty (CPP). CPP occurs at least 10-fold more frequently in girls than in boys; in more than 90% of girls, PP is predominantly idiopathic[2]. It is estimated that precocious puberty affects between 1 in 5,000 and 1 in 10,000 children, and a recent study showed there was a tendency of increasing incidence in girls[3]. However, CPP may be secondarily related to brain tumors, congenital brain defects, brain injuries, early exposure to sex steroids, and untreated hypothyroidism[4]. Peripheral or gonadotropin-independent precocious puberty may be due to gonadal or adrenal tumors or premature activation of the gonadotropic pathway. McCune-Albright syndrome is also a rare cause of peripheral precocious puberty[5].

CPP is far less common in children before 3 years of age, particularly in females. Most girls with signs of puberty less than 3 years of age are diagnosed with premature thelarche (PT), which is a benign and non-progressive condition[6]. To date, no laboratory variable has been found to predict which girls with PT will eventually develop CPP. We present a rare idiopathic CPP before 3 years of age present idiopathic CPP before 3 years of age who presented with PT that rapidly progressed to CPP, and review the frequency of diagnoses in children less than 3 years of age for early puberty and the useful predictors of pubertal progression.

Correspondence to : Kyung-Sue Shin
Department of Pediatrics, Jeju National University School of Medicine, 15, Aran 13gil, Jeju-si, Jeju Special self-governing province, 63241, Republic of Korea
E-mail : kyungsue@jejunu.ac.kr

CASE REPORT

A seventeen-month-old girl was referred to pediatric outpatient clinic with an increasing breast enlargement followed by the development of pubic hair, and brown vaginal discharge. Three month prior to the current presentation, she had minimal breast budding and had been recommended to the pediatric endocrinology for evaluation of puberty. She had been born at 39 weeks gestation by vaginal delivery with birth weight 2.88 kg. Her family history was negative for developmental anomalies. On physical examination, she was 75th percentile for height and 95th percentile for weight. Pubertal staging according to Tanner's method[7] was assessed at B2, P1, and A1.

Laboratory evaluation was significant for an elevated estradiol of 70.2 pg/mL, and elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH); 3.6

IU/L and 8.8 IU/L, respectively. Thyroid studies and prolactin levels were normal. The levels of dehydroepiandrosterone sulfate (DHEA-S) and 17-hydroxyprogesterone (17-OHP) were also appropriate for her age. Bone age was advanced by over two year (4.1 years of age) using the method of Greulich and Pyle[8] (Fig. 1). Gonadotropin releasing hormone (GnRH) stimulation test was arranged. A standard dose of 100 μg GnRH (Relefact®) was administered as an intravenous (IV) bolus. An IV cannula was inserted and blood samples were obtained before the injection and at 15, 30, 45, 60, 90, and 120min after the injection. The peak LH level was achieved 30min after GnRH stimulation (66.4 IU/L) and the peak LH/FSH ratio was greater than 1.0 (4.2 at 30 min). GnRH stimulation test revealed elevated levels of gonadotropins and appropriate for a pubertal female.

Computed tomography of pelvis showed an enlarged uterus for age, and the right ovary was of normal size, but the left ovary was enlarged, measuring 1.6 x 1.7 cm (ovarian volume: 2mL) (Fig. 2). Brain and pituitary MRI showed a normal pituitary gland with a mild elongated height compatible with the change of CPP, but no other organic causes for CPP were detected (Fig. 3).

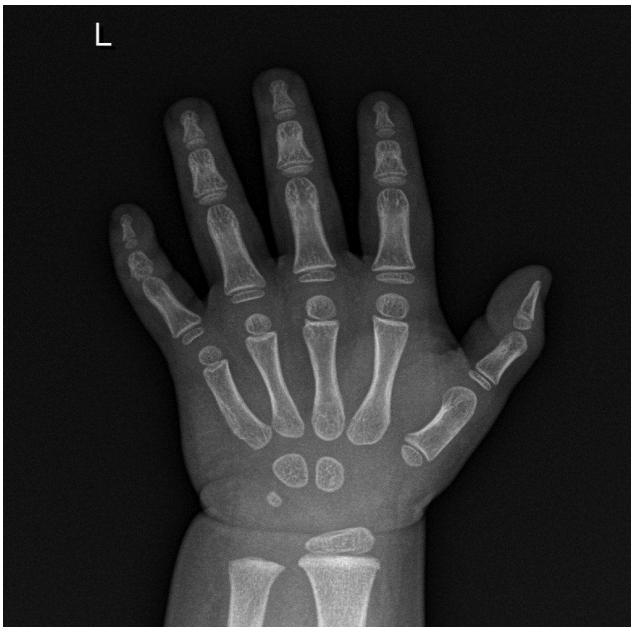

Figure 1. Bone age of patient
Bone age was 4.1 years of age using the method of Greulich and Pyle.

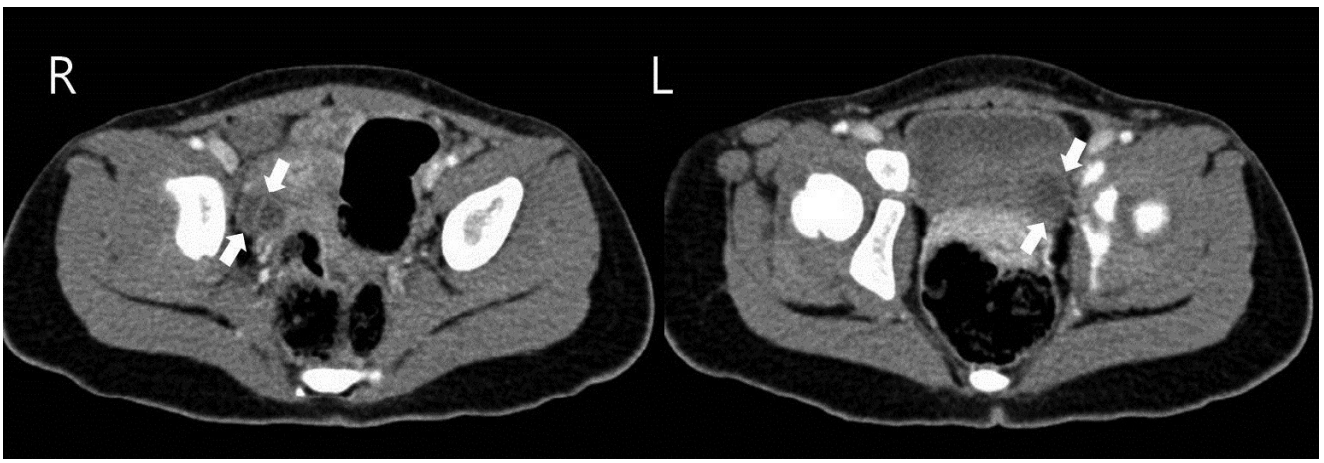

Figure 2. Computed tomography of pelvis
Computed tomography of pelvis showed an enlarged uterus for age, and the right ovary was of normal size, but the left ovary was enlarged, measuring 1.6 x 1.7 cm (ovarian volume: 2 mL).

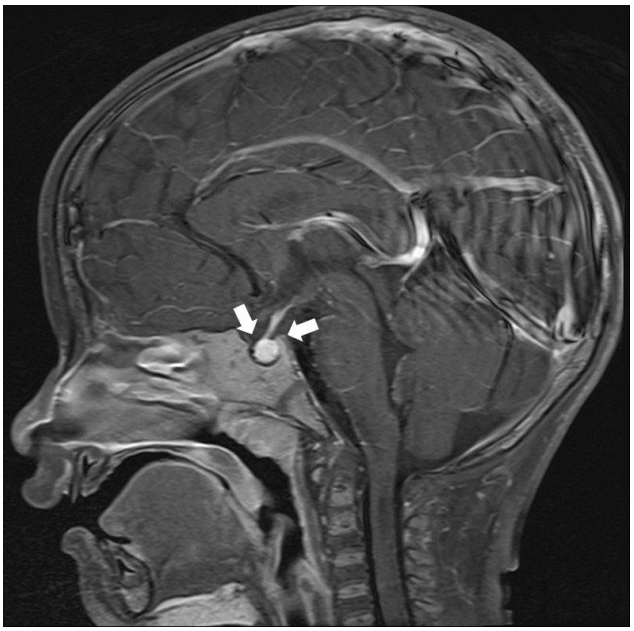

Figure 1. Magnetic Resonance Imaging of sella
Brain and pituitary MRI showed a normal pituitary gland with a mild elongated height compatible with the change of CPP, but no other organic causes for CPP were detected.

Treatment with the GnRH agonist (Leuprorelin®) was initiated, and she was managed with at the dosage of 1.875 mg (120 ug/kg) every four weeks for 6 months. Laboratory follow-up after 6 months revealed normal low levels of gonadotropins with no physical signs of progressing puberty. After 6 months of total treatment, we and the family decided to discontinued therapy and monitor for symptoms of puberty progression instead of continuing therapy. Currently, her puberty has stabilized and signs of puberty are no longer present.

Discussion

The normal range for pubertal development, defined as 8-13 years of age, was established in the 1960s[9]. Because the onset of puberty may begin earlier, the Lawson Wilkins Pediatric Endocrine Society recently recommended the evaluation for PP in girls with signs of puberty should be undertaken before age 6 or 7 years[10]. However, many researchers have used the traditional age cut-off of 8 years for PP in girls.

Children with signs of puberty before 3 years of age have been found to have significant pathology less often than in children older than age 3, because CPP is far less common in very young children than in 6-8 year olds. Particularly, most girls with signs of puberty before 3 years of age are generally diagnosed with premature thelarche (PT). PT is defined as isolated breast development in girls less than 8 years of age[11]. Although the etiology of PT is unclear, increased sensitivity of breast tissue to estradiol (E2), transient ovarian cysts, iatrogenic estrogen intake, and transient activation of the HPG axis have been proposed as possible mechanisms[12]. The other sign of puberty less than 3 years of age is the appearance of fine hair in the genital area, typically along the labia in girls and on the scrotum in boys. This has been known to as genital hair of infancy (GHI), and is apparently different from the suprapubic distribution of genital hair seen in children with premature adrenarche[6]. In recent study, the GHI patients had mildly elevated DHEA-S but normal testosterone and 17-OHP; therefore hormone testing is not to be helpful in differential diagnosis of GHI[6].

However, the possibility of progression of PT to CPP has not been well established. Some studies found that girls with PT had normal puberty and did not progress to PP[13, 14]. Other studies showed that PT may progress to PP at a variable rate, from 3.2% to 18.4%[15,16]. The association between age of PT onset and progression to PP also remains unclear. Some studies demonstrated such an association with older age at PT presentation, mostly after age 2, but others failed to do so[11-16]. In a recent cohort in Israel[15], risk of PP was similar in all girls with PT, regardless of age at onset. There were no clinical or laboratory tests that can predict the risk of progression to PP at presentation. In this report, she was already represented with PT prior to visit our clinic and PT was rapidly progressed to CPP only within 3 months. Up to date, it is until unsolved problem why her signs of puberty were rapidly progressed and what are the useful predictors of pubertal progression[17]. Simple premature thelarche may develop into precocious or early puberty. The patients with pubertal progression are not to be confused with the thelarche variant described by Stanhope and Brook[18] and the exaggerated thelarche described by Garibaldi et al[19]; their patients failed to respond to GnRH analog treatment, whereas our patient responded clinically and hormonally like patients with CPP.

In conclusion, we report idiopathic CPP before 3 years of age who presented with PT that rapidly progressed to CPP. Based on our observations, premature thelarche may not always be a self-limited condition. Because currently there are no predictive clinical or laboratory tests that can identify

the risk of progression to PP at time of onset, all girls with PT should be monitored clinically for accelerated pubertal progression.

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