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Case Report / Olgu Sunumu

# Phenylketonuria and Puberty Precoccious Association; A Case Report

## Fenilketonüri ve Puberte Prekoks Birlikteliği: Bir vaka sunumu

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**Abstract:** Phenylketonuria (PKU) is one of the most common preventable causes of intellectual disability resulting from deficiency of phenylalanine hydroxylase enzyme activity. Precocious puberty (PP) is characterized by premature breast and pubic hair development, and advanced bone age development before 8 years of age for girls and 9 years of age for boys. We present a 7 years old girl with phenylketonuria and overweight, who has developed early puberty. PKU was confirmed by plasma amino acid analysis at newborn.At the age of 7, the first signs of PP appeared (T3). Laboratory tests were detected as luteinizing hormone 0.36 mIU/mL; follicule stimulating hormone 1.1 mIU/mL; estradiol 20 pg/mL; and bone age was 9 years. The response to gonadotropin-releasing hormone stimulation test was characteristic for true PP (LH 5.4 mIU/mL; FSH 8 mIU/mL). According to our current knowledge, the reason for this union isn't clear. However, this association may be incidental or secondary to overweight and may also be secondary to phenylketonuria - good / bad metabolic control. It's thought that PP cases may be seen more frequently due to the increase of obesity frequency in PKU patients.

**Keywords:** Phenylketonuria, central puberty precocious, overweight, obesity

**Özet:** Fenilketonüri (FKÜ), fenilalanin hidroksilaz enzim aktivitesinin eksikliğinden kaynaklanan zihinsel engelliliğin en yaygın önlenebilir nedenlerinden biridir. Puberte prekoks (PP), kızlarda 8 yaşından önce ve erkeklerde 9 yaşından önce; erken meme gelişimi ve pubik kıllanma ile ileri kemik yaşı gelişimi ile karakterizedir. Bu yazıda PP gelişen fenilketonüri tanılı ve aşırı kilolu 7 yaşında bir kız hasta sunulmaktadır. FKÜ tanısı yenidoğan döneminde plazma amino asit analizi ile doğrulandı. 7 yaşında, PP'nin ilk belirtileri ortaya çıktı (T3). Laboratuvar testleri, luteinize edici hormon 0.36 mIU / mL; folikül uyarıcı hormon 1.1 mIU / mL; estradiol 20 pg / mL; kemik yaşı 9'du. Gonadotropin salgılatıcı hormon stimülasyon testine yanıt, gerçek PP (LH 5.4 mIU / mL; FSH 8 mIU / mL) için karakteristikti. Mevcut bilgilerimize göre, bu birliğin nedeni açık değildir. Bununla birlikte, bu ilişki tesadüfi ya da fazla kiloya ikincil olabilir ve fenilketonüri - iyi / kötü metabolik kontrole ikincil olabilir. FKÜ hastalarında obezite sıklığının artması nedeniyle PP vakalarının daha sık görülebileceği düşünülmektedir.

**Anahtar Kelimeler:** Fenilketonüri, puberte prekoks, kilo fazlalığı, obezite

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## 1. Introduction

Phenylketonuria is one of the most common autosomal recessive inherited disorders of amino acid metabolism. It is caused by phenylalanine hdyroxylase enzyme deficiency (1). It results accumulation of phenylalanine (Phe) in blood and other body fluids. If treatment is not effectively initiated soon after birth, PKU may lead to severe intellectual disability, seizures, behavioral problems, and mental disorders (2). It was first described by Asbjorn Folling in 1934 by detecting phenylketones in the urine of siblings with mental retardation (1). Classification of the severity of PKU is based on the type of the genetic mutations in phenylalanine hydroxylase (PAH) gene, pretreatment blood Phe concentrations and dietary Phe tolerance (2). Untreated, late-treated, or poorly controlled patients have chronically eleveted blood Phe concentrations. Symptoms of persistent hyperphanyalaninemia are progressive and irreversible neurological, psychological, behavioral, as well as physical impairments that significiantly impact quality of life. Conversely, early and continuously treated patients typically have normal or nearly normal cognitive development. Newborn screening data show that the overall incidence of PKU is about 1 in 10,000-30,000 live births in Europe, and 1 in 3,500 to 5,000 in Turkey due to high consanguinity (3,4).

Precocious puberty (PP) means to the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal. Puberty is considered precocious in girls younger than 8 years; in boys before 9 years (5). The estimated incidence of PP is 1:5.000-10.000 throughout the world with a female:male ratio > 10:1 (6). If the history, physical examination, and laboratory data suggest that a child exhibits early evidence of pubertal maturation, the clinician must differentiate central precocious puberty (CPP) from precocious pseudopuberty. Central PP, which is gonadotropin-dependent, is the early maturation of the entire hypothalamic-pituitary-gonadal (HPG) axis, with the full spectrum of physical and hormonal changes of puberty. Precocious pseudopuberty is much less common and refers to conditions in which increased production of sex steroids is gonadotropin-independent. Early activation of the hypothalamic-pituitary-gonadal axis in PP is mostly idiopathic, especially in girls (5). However PP may be secondarily related to brain tumors (hamartoma especially), congenital brain defects, brain infections, cranial irradiation, insults and injuries to the brain or spinal cord (including cerebral palsy, hydrocephalus and brain ischemia) and obesity (7). Central PP and phenylketonuria are two rare conditions. There has been three previous reports including four patients with the association between phenylketonuria and puberty precocity; so to our knowledge this is the fifth case of phenylketonuria associated with CPP in a female subject.

## 2. Case Report

A seven year-old girl patient was admitted to our clinic with a 6 months history of breast development. Development of pubic hair, body odour and brown vaginal discharge were not found. The female patient was born following a normal pregnancy and normal birth weight. The parents were second degree relatives. Newborn screening revealed HP with a Phe level of 1680 µmol/L on day nine. Severe hyperphenylalaninaemia had been confirmed with plasma amino acid analysis (2160 µmol/L) and she was started on dietary treatment from day nine of life. Sequence analysis of the PAH gene identified two heterozygote mutations: c.781C>T (p.Arg261Ter) and c.782G>A (p.Arg261Gln) which are associated with a severe phenotype. From infancy to one year old, the girl underwent weekly Phe measurements with median values of 300 µmol/L (22.8–810). After than Phe check was done once a month. Her blood Phe concentrations were well controlled and ranged 120-360 µmol/L during a follow-up period of 7 years. She showed normal neurodevelopment. She had no history of head injury, encephalitis, headache or seizures. General physical examination of the patient was within normal limit. Her weight was 30.5 kg (90. percentile), her height was 124 cm (75. percentile), body mass index

(BMI) was 19.8 (90-95.percentile) and skin pigmentation was absent.

There was obvious physical development beyond her chronological age with the evidence of breast development; she was Tanner stage 3, no menarche. Her bone age was 9 years. Laboratory results were detected as follows: luteinizing hormone (LH), 0.36 mIU/mL; follicle-stimulating hormone (FSH) 1.1 mIU/mL; estradiol 25pg/mL. The peak LH and FSH to luteinizing hormone releasing hormone (LHRH; gonadotropin releasing hormone stimulation test) were all within the pubertal range at 5.4 mIU/mL and 8 mIU/mL, respectively. The serum estradiol level was 25 pg/mL, which is higher than the normal level in her age group (reference range, 2–15 pg/m). Abdominopelvic ultrasound revealed a normal adult-sized uterus with a maximal anteroposterior (AP) diameter of 47 mm. The patient was diagnosed with central PP, based on the elevated serum levels of LH, FSH and subsequent elevations in sex steroids, having been thoroughly examined by pediatric endocrinologists. All other pituitary hormone levels were found within the normal range. Brain MRI showed a normal pituitary gland and any intracranial lesion. These findings are consistent with the diagnosis of idiopathic PP. Our patient has been successfully treated with a GnRH analogue.

## 3. Discussion

Phenylketonuria was the first inherited metabolic disease identified by newborn screening. It is a leading cause of preventable intellectual disability world wide. Dietary restriction of phenylalanine remains to be the cornerstone of treatment for PKU since its introduction in 1953 by Bickel and colleagues (8). Patients with PKU must strictly limit their intake of foods rich in protein, such as meats, fish, eggs and dairy products. Low-protein high-starch natural foods such as potatoes, some vegetables (such as peas) can be eaten but only in restricted amounts. Due to the severe restriction of protein intake, PKU patients must be supplemented with medical food substitutes containing the right mix of essential amino acids, vitamins, minerals and trace nutrients (9). There commendation was to continue life-long diet therapy.

Our patient has a severe hyperphenylalaninaemia with a low phenylalanine tolerance. Her parents achieved an excellent dietary control of Phe concentrations, consistently within there commended range with subsequent normal neurodevelopment. To our knowledge, there is only one previous case reported by Lucaccioni (10) describing CPP in a 3.2 years old PKU girl with a 12 months history of breast and pubic hair development, and vaginal discharge whose blood phenylalanine concentrations were persistently well controlled as our patient. The authors conclude that CPP is a rare coincidental event in children with PKU and can occur independently by the persistently high phenylalanine concentrations. Conversely, Buyukgebiz et al. reported a 7.5 years old girl PKU patient with premature telarche. Her serum phenylalanine levels were high due to poor compliance with the phenylalanine restricted diet and it may be related to the early onset of puberty (11).

Recent data suggest that excess adiposity during childhood may influence pubertal development. Childhood obesity, a result of relative over nutrition, has become a major health concern in recent decades. Early breast development may in part reflect increased peripheral aromatization of adrenal androgens in an expanded adipose tissue compartment. Hyperinsulinemia may play a prominent role in this regard. Body fat makes estrogens, which are the same kind of hormone that are normally released from the ovaries during puberty (12). Diet treatment for PKU includes a diet restricted in Phe and an amino acid-based medical food devoid of Phe. Thats why PKU patients tend to consume a diet enriched in carbohydrates which could predispose to obesity. There is a trend for a higher rate of obesity in girls, as previously reported (13,14). Conversely, Rocha et al. (15) reported that patients with PKU and controls were similar in terms of overweight and obesity. Our patient's body mass index was calculated to be 19.8 (90-95.percentile). According to the curves of the centers for

disease control and prevention (CDC), overweight was detected. Our patient has been overweight for the past four years.

There is a lack of evidence for different timing of pubertal onset in PKU patients compared with the general population. We conclude that early puberty rates in patients with phenylketonuria may increase in the future because overweight in PKU is increasing like general population. We wanted to emphasize the importance of weight management in PKU patients with two rare conditions.

In conclusion, the association of CPP and PKU has been reported previously in the literature, and further experience is needed for its elucidation. As the neuroendocrinological mechanisms in PKU are not clear, we are of the opinion that further experiences are required to clarify whether this association may be coincidental, secondary to overweight and may also be secondary to phenylketonuria - good / bad metabolic control. It is thought that puberty precocious cases may be seen more frequently due to the increase of obesity frequency in phenylketonuria patients.

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