

A rare endocrinological complication of chronic kidney disease

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ABSTRACT

Background. Chronic kidney disease (CKD) may lead to increase in serum levels of peptide hormones as a result of changes in peripheral metabolism. The pathogenesis of uremic hyperprolactinemia in CKD is not fully understood. Plasma prolactin levels are elevated in women, pubertal girls, and also in men with chronic kidney disease. But this is not common in prepubertal boys. Also in prepubertal children and postmenopausal women, hyperprolactinemia rarely results in galactorrhea. We aimed to discuss hyperprolactinemia and galactorrhea in a 12-year-old male with CKD.

Case. A twelve-year-old boy with chronic kidney disease (CKD) suffered from bilateral galactorrhea. He was on follow-up at Pediatric Nephrology Department from the age of two due to bilateral dysplastic kidney. On physical examination, his weight was - 0.59 SDS, height was -2.82 SDS, Blood pressure was 115 / 72 (75p), stretched penis length was 6 cm, testicular volume was 3mL / 3mL, pubic hair was Tanner Stage 1, breast examination did not reveal plaque on bilateral breast. He was receiving recombinant erythropoietin, sodium bicarbonate, polystyrene sulfonate, calcium acetate, and calcitriol treatments. Glomerular filtration rate was 23ml/min/1.73 m² (CKD stage IV). Serum prolactin (PRL) was >200 µg/L (N, 2.64-13.13). The pituitary adenoma was excluded with pituitary and cranial magnetic resonance imaging (gadolinium). Cabergoline (0.5 mg/ twice weekly) was initiated to decrease PRL levels and reduce galactorrhea. In the second week of treatment, serum PRL level was suppressed (0.4 µg/L) and galactorrhea was completely resolved.

Conclusions. Although uremic hyperprolactinemia is very rarely seen in childhood, it is important to evaluate, and initiate an appropriate treatment since it is associated with delayed puberty and infertility in adulthood in many cases.

Key words: children, chronic kidney disease, galactorrhea, hyperprolactinemia.

Many metabolic and endocrinological abnormalities are encountered in chronic kidney disease (CKD). Studies showed that decrease in glomerular filtration rate, and change in the metabolic environment due to uremia can cause impaired extrarenal metabolism and integrity of feedback controls regulating secretion or synthesis of the peptide hormones.¹

Prolactin (PRL) is responsible for the hormonal regulation of lactation and regulation of gonadal luteinizing hormone receptors in both genders. PRL also has many physiological functions such as osmoregulation, immune response and angiogenesis.¹ The pathogenesis of uremic hyperprolactinemia in CKD is not fully understood. In prepubertal children and postmenopausal women, hyperprolactinemia rarely results in galactorrhea.² Galactorrhea is not an expected finding in prepubertal cases. We aimed to discuss hyperprolactinemia and galactorrhea in a 12-year-old male with CKD.

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Case Report

A twelve-year-old boy with chronic kidney disease (CKD) suffered from bilateral galactorrhea. He was on follow-up at Pediatric Nephrology Department from the age of two due to congenital anomalies of kidney and urinary tract (congenital bilateral dysplastic kidney). In his medical history; he was born at 40 weeks' gestation with a birth weight of 3100 g and there was a hospitalization in the neonatal intensive care unit because of asphyxia. He received antibiotic therapy many times due to recurrent urinary tract infection. He had no vesico ureteral reflux. 99mTc dimercaptosuccinic acid (DMSA) scan show only bilateral small kidneys. On physical examination, his weight was 37.2 kg (-0.59 SDS), height was 128.6 cm (-2.82 SDS), z-score of body mass index (BMIz score) +1.01 SDS, target height 172.1 cm (-0.61 SDS), blood pressure was 115/72 mmHg (75/75p), stretched penis length was 6 cm, testicular volume was 3mL/3mL, and pubic hair was at Tanner stage I. Breast examination did not reveal plaque or gynecomastia but galactorrhea was noted. Other systems and neurologic examinations were normal. Bone age according to Greulich- Pyle was 10 years and predicted adult height was calculated as 160 cm (-2.27 SDS) by the Bayley-Pinneau method. He was receiving recombinant erythropoietin, sodium bicarbonate, polystyrene sulfonate, calciumacetate, and calcitriol treatments. Glomerular filtration rate was 23 ml/min/1.73 m² (CKD stage IV). Laboratory investigations revealed; Hb 10.2 g/dL, blood urea 152 mg/dL, creatinine 3.9 mg/dL, calcium 10.5 mg/dL, phosphate 6.1 mg/dL, alkaline phosphatase 264 mg/dL (160-500), 25-hydroxy vitamin D 32 µg/L (N, 20-100), parathyroid hormone 182 ng/L (N, 10-69), free T4 0.82 ng/dL (N,0.54-1.24), thyroid-stimulating hormone 3.2 mIU/L (N, 0.34-5.6), luteinizing hormone(LH) 1 mIU/mL (N, <0.1), follicle stimulating hormone 2.8 IU/L (N, 0.1-4.3), total testosterone 10.3 ng/dL (N, <20), PRL>200 µg/L (N,2.64-13.13), and somatomedin-C (IGF-1) 168 g/L (N, 68-316). Pituitary and cranial magnetic resonance imaging with gadolinium showed

no intracranial pathology. Pre-emptive renal transplantation was planned in our patient. However, peritoneal dialysis was started since no suitable donor could be found. Cabergoline (0.5 mg/ twice weekly) was initiated to decrease PRL levels and reduce galactorrhea. In the second week of treatment, serum PRL level was suppressed (0.4 µg/L) and galactorrhea was completely resolved. Informed consent was received from the parents.

Discussion

Decrease in renal function causes changes in the synthesis, secretion, metabolism, and elimination of peptide hormones.³ Deranged metabolic environment of uremia may contribute to impaired metabolism which regulates the integrity of feedback controls regulate the synthesis of secretion.² Elimination of PRL occurs both through glomerular filtration and tubular breakdown.² PRL is reabsorbed by tubular cells by blood flowing in peritubularcapillaries from the anti-luminal pole of proximal tubular cells.⁴ The pathogenesis of uremic hyperprolactinemia in CKD is not fully understood. Chronic renal failure stimulates dysregulation of PRL secretion by a resistance of lactotrophs to dopaminergic inhibition.⁵

Plasma PRL correlates with serum creatinine levels; as the renal functions deteriorate, PRL level increases. Therefore, hyperprolactinemia is seen in patients with CKD with advanced or even end-stage renal failure. Peces et al.¹ reported that patients diagnosed with CKD who have hemodialysis had higher PRL levels compared to healthy controls and patients who had undergone kidney transplantation. The serum PRL levels in women were higher than in men in this study. In a study conducted by Ijaiya et al.⁵ it was reported that serum PRL levels in children with acute renal insufficiency and renal transplantation were similar to healthy children, while those with chronic renal failure were 2.5 times higher. Moreover elevated basal PRL could not be stimulated by TRH stimulation.⁵

Dysfunction due to vitamin D deficiency, anemia, zinc depletion and pituitary regulation of PRL release can be the other etiological factors resulting in hyperprolactinemia in CKD patients.^{6,7} The presence of inflammatory cytokines and chronic metabolic acidosis may contribute to dysregulation of the hypothalamic-pituitary-thyroid axis in CKD.⁶ Pathological thyroid profile, including clinical or subclinical hypothyroidism, can also cause alterations in the hypothalamo-hypophyseal-gonadal axis and can manifest with hyperprolactinemia.⁶ Thyroid function tests should be evaluated in cases with hyperprolactinemia. Thyroid function tests, vitamin D and hemoglobin were normal in our patient. Many antipsychotic drugs increase PRL levels by affecting the dopaminergic system. Methyldopa and verapamil used in the treatment of hypertension are other causes of drug-related hyperprolactinemia.⁸⁻¹⁰ Gulleroğlu et al.⁹ reported an eleven-year-old boy on peritoneal dialysis with galactorrhea. He was using methyldopa for hypertension so they thought that galactorrhea was related to methyldopa instead of uremia as he was already on renal replacement therapy for long-term. Tacrolimus and amlodipine-induced hyperprolactinemia has been reported in a 19-year-old woman with kidney transplantation who presented with galactorrhea and mastalgia.¹⁰ The medications of our patient were questioned in detail, but there were no agents causing drug-related hyperprolactinemia. Cases with chronic kidney disease and hyperprolactinemia reported in the literature are summarized in Table I.

Hyperprolactinemia is defined as an increase in serum prolactin levels. Normal prolactin levels are $< 25 \mu\text{g/L}$ in girls, and $< 20 \mu\text{g/L}$ in boys.¹¹

Plasma prolactin levels are elevated in women, pubertal girls, and also in men with chronic kidney disease.¹²

This situation is not usual in prepubertal boys. Our case was prepubertal according to testis volume, however, high levels of basal LH was incompatible with the prepubertal period. Hypothalamic and hormonal causes were excluded, so hyperprolactinemia in our patient was attributed to uremia. Our patient was clinically prepubertal, therefore, we focused primarily on a possible PRL-secreting adenoma. PRL levels $> 200 \mu\text{g/L}$ are highly related to secretion PRL by prolactinoma.¹³ Pituitary imaging is recommended for symptomatic patients.¹⁴ Therefore, the patient was evaluated for pituitary adenomas by the pituitary and cranial magnetic resonance imaging. However, there were no findings related to pituitary compression, and no adenoma or tumor was found on MRI. Hyperprolactinemia can cause gonadotropin suppression, anovulation, irregular menstrual cycles, infertility, hypoestrogenism, gynecomastia, sexual dysfunction and galactorrhea in adults.^{3,14} Male patients usually show intracranial pressure symptoms such as headache and visual loss due to tumor growth.¹⁴

Disturbances in the control of hypothalamic-pituitary-gonadal axis in men and women with CKD and end-stage renal disease is well-known; however, it is not fully understood. Delayed puberty and reduced pubertal growth are very pronounced in children with CKD due to long-term dialysis treatment and high glucocorticoid exposure.¹⁵ Hyperprolactinemia also contributes to this situation by decreasing pulsatile gonadotropin-releasing hormone secretion and

Table I. Cases reported in the literature with hyperprolactinemia and chronic renal diseases.

Cases	Age	Gender	Renal status	Suspected etiology
Bry-Gauillard ¹⁷	34	male	Hemodialysis	Macroadenoma of the hypophysis
Pratap ⁷	42	female	Hemodialysis	Methyldopa
Khira ⁹	19	female	Renal tx	Tacrolimus, amlodipine
Rondeau ²	4	female	Hemodialysis	Chronic kidney disease
Gulleroğlu ⁸	11	male	Periton dialysis	Methyldopa

thus inhibiting luteinizing hormone (LH) and follicle-stimulating hormone secretion as well as gonadal steroidogenesis (hypogonadotropic hypogonadism).¹¹ In uremic patients, despite decreased LH secretion from the pituitary gland, serum LH concentration may be elevated due to impaired renal clearance, but bioactivity of LH is decreased.¹⁶ Interestingly, central precocious puberty was also reported in girls and boys with CKD.¹⁶⁻¹⁸ Furthermore, a case of precocious puberty associated with hyperprolactinemia was also reported.¹⁹ The authors hypothesized that high prolactin levels might have both stimulated and inhibited the hypothalamic-pituitary-gonadal axis.¹⁹ In brief, the pathophysiology of neuroendocrine dysregulation in uremic patients remains unclear. Despite the increased LH level, our patient's testicular volumes, serum total testosterone level and bone age were compatible with the prepubertal period. Besides, following normalization of PRL levels with cabergoline treatment, LH levels decreased to 0.5 mIU/mL and no progression in pubertal findings was observed at clinical follow-up.

Hyperprolactinemia treatment varies according to the underlying etiology. The main objectives of treatment are normalizing prolactin level, reducing the diameter of the adenoma and reducing clinical signs related to hyperprolactinemia.^{11,14,15} The reduction of the drug dose or transition to another drug is enough for the treatment of drug-induced hyperprolactinemia.¹⁴ Dopamine agonists are a successful therapeutic option in prolactinomas. Cabergoline has been shown to be more effective in normalizing prolactin levels and reducing tumor size with fewer adverse effects than bromocriptine.¹³ A significant tumor shrinkage can be achieved with cabergoline in microadenomas (<10 mm), whereas surgery may be needed in addition to cabergoline treatment in macroprolactinomas (> 10 mm). In uremic hyperprolactinemia, it may be beneficial to start renal replacement therapy due to the

contribution of uremia. Renal replacement therapies should be considered to eliminate the uremic state in hyperprolactinemia due to CKD. However, in the literature, hyperprolactinemia has been reported in cases receiving peritoneal dialysis. Frequent hemodialysis sessions did not decrease the prolactin levels.²⁰ Bilateral nephrectomy was performed in a 4-year-old girl with an end-stage renal failure due to uncontrolled severe hypertension. PRL levels rose following bilateral nephrectomy. After kidney transplantation, PRL levels decreased dramatically in 8 hours in this patient. Authors suggest that even uremic kidneys can eliminate PRL through tubular breakdown since PRL levels increase after bilateral nephrectomy.² After renal transplantation, hyperprolactinemia can usually be corrected or significantly improved.²¹ It has been reported that PRL levels decrease or return to normal levels with the increase of glomerular filtration rate after kidney transplantation.⁵ It has been demonstrated repeatedly that serum PRL levels rapidly return to normal after kidney transplantation, as in the cases reported in the literature.^{8,22,23}

Early renal transplantation in the pediatric population has demonstrated adequate pubertal developmental outcomes. Therefore, the most appropriate approach is to find a suitable donor for the patient and perform renal transplantation. Although uremic hyperprolactinemia is very rarely seen in childhood, it is important to evaluate, and initiate an appropriate treatment since it is associated with delayed puberty and infertility in adulthood in many cases.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SAÇ; data collection: BF, ES, DA; analysis and interpretation of results: HM, GÇ, FM; draft manuscript preparation: SAÇ, BND, BKD. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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