

## Case Report

# Serum prolactin levels in a uremic child: effects of bilateral nephrectomy and kidney transplantation

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### Abstract

Elevated levels of serum prolactin (PRL) are common and well described in patients with chronic renal failure. We report the case of a 4-year-old girl who also presented with premature thelarche and transient galactorrhea. Neither peritoneal dialysis nor hemodialysis reduced her extremely elevated levels of PRL, which fluctuated from time to time, probably reflecting variations in lactotroph secretion rate. Bilateral nephrectomy (BN) was eventually followed by a progressive and significant rise in PRL levels, suggesting that even uremic kidneys can eliminate PRL through tubular breakdown. Kidney transplantation was responsible for a very abrupt normalization of PRL serum levels, much faster than that observed for creatinine. This confirms animal studies suggesting that elimination of PRL occurs both through glomerular filtration and tubular breakdown. We hypothesized that the seemingly precocious puberty may have resulted from a combination of growth hormone therapy, elevated PRL and a rise in estrogens through the aromatization of adrenal androgens. This case illustrates the impact of dialysis, BN and kidney transplantation on PRL, providing new knowledge on renal PRL metabolism.

**Keywords:** bilateral nephrectomy; dialysis; kidney transplantation; prolactin; uremia

### Introduction

Elevated levels of serum prolactin (PRL) are common in patients with chronic renal failure, described both in adults [1, 2] and children [3]. When present prior to dialysis, elevated serum PRL persists through hemo- and peritoneal dialysis [3], sometimes reaching levels of 300–400 µg/L. After renal transplantation, concentrations have been shown to normalize [4, 5]. Elevated PRL is well documented in both men and women with uremia, where it is associated with signs and symptoms such as menstrual disturbances, infertility, loss of libido and gynecomastia [6]. Here, we report the case of a 4-year-old girl with uremia and marked hyperprolactinemia associated with transient thelarche and

galactorrhea. Following bilateral nephrectomy (BN), PRL levels rose significantly and then abruptly normalized soon after kidney transplantation. The observed PRL levels provided new knowledge regarding renal excretion and metabolism of this hormone.

### Case report

A 44-month-old girl was admitted with a history of puffiness of the eyelids and frequent headaches over the past few weeks. On examination, she was found to have periorbital edema, pitting edema of the ankles and severe hypertension with a widened pulse pressure (160/70 mm Hg). She was the first of three children of non-consanguineous Caucasian parents, neither of whom had any significant history of renal disease or precocious puberty. Laboratory results revealed a markedly elevated serum creatinine of 487 µM/L. Her urine output was reduced to ~500 mL/day. She was started on thrice weekly hemodialysis. Verbal consent to use clinical information for publication was obtained from the parents and approved by our local ethics committee. A renal biopsy showed severe focal and segmental glomerulosclerosis with capillary collapse and mesangial sclerosis. Analyses for associated gene mutations (nephrine, podocin and Wilms' tumor suppressor gene WT1) were negative. After 1 month of hemodialysis at the family's request, she was switched to peritoneal dialysis dispensed by a cyclor 6 nights a week.

Four months after her initial admission, the patient developed anuria. She underwent BN 3 months later because of uncontrolled hypertension. Postoperatively, no hypertensive medication was necessary. Two months after the surgery, at the age of 50 months, the mother noticed the child's nipples becoming rapidly more prominent. On manual palpation during a medical examination, 3 weeks after this first observation, galactorrhea was noted. Nipple budding and galactorrhea lasted for 2 months before gradually subsiding. There was no acceleration of linear growth and bone age estimate was concordant with chronological age. Pituitary–thyroid and pituitary–adrenal axis functions were normal. On pelvic magnetic resonance imaging (MRI), there were signs of

slight ovarian enlargement and endometrial stimulation, while a gonadotropin-releasing hormone (GnRH) stimulation test showed a prepubertal response. It was felt that the cause of premature thelarche was perhaps due to an unsustained precocious puberty. Moreover, clinical signs occurred concomitantly with the onset of human growth hormone (GH) therapy. A brain MRI was normal.

We used a radioimmunoassay (Prolactin Access 33530; Beckman Coulter, Inc, Brea, CA) on blood samples leftover from previous blood work to compare PRL levels pre- and post-BN (Figure 1). PRL rose progressively >4 months following BN and remained high (300–400 µg/L) until the eve of a kidney transplantation at age 71 months.

Within 8 h of the living donor kidney transplant, the serum PRL concentration fell dramatically to almost normal levels, and by 24 h, normal levels were reported (Figure 2). Plasma creatinine levels dropped from 400 to 225 µM/L within 8 h and normalized at 50 µM/L after 72 h. Urine output during these first 3 days was excellent, averaging >3 L/day.

It is noteworthy that during the entire observation period, the child received no medication susceptible of affecting PRL levels, such as dopamine antagonists, calcium channel blockers or verapamil. She was given 0.15 µg calcitriol (vitamin D3) throughout this period up until the time of transplantation. The average daily dose was of 0.15 µg daily until the time of transplantation, except between ages 50 and 58 months when the dose was increased to 0.50 µg/day. She received subcutaneous human GH injections at a dose of 0.05 mg/kg, 6 days a week throughout this period except for the 3 weeks following the appearance of galactorrhea; therapy was stopped 1 week prior to transplantation.

Serum parathyroid hormone levels measured monthly, varied markedly from 1.9 (low normal) to 75.6 pM/L, until the time of kidney transplantation. The highest values were observed in the first 4 months of peritoneal dialysis. No significant correlation was found between serum PRL and parathyroid hormone levels using the Pearson correlation test ( $P = 0.803$ ).

## Discussion

Chronic renal failure often results in delayed sexual maturation in adolescents. Nonetheless, two reports in the literature described central precocious puberty in young boys, which appeared to be fully reversible following successful renal transplantation [7]. The endocrine findings (high testosterone, high gonadotropins and a pubertal response to GnRH stimulation) combined with normal cranial MRI results were suggestive of unexplained hypothalamic dysregulation. In the present case, precocious thelarche and galactorrhea in a 4-year-old girl prompted an endocrinological investigation which allowed us to incidentally observe PRL levels under conditions including uremia, BN and kidney transplantation.

Our patient presented with detectable levels of estradiol but a clearly prepubertal response to the GnRH stimulation test, thus eliminating true central precocious puberty from the differential. The presence of galactorrhea, however, added credence to the estrogen finding, regardless of PRL levels. In postmenopausal estrogen-deficient women and prepubertal children, hyperprolactinemia rarely results in galactorrhea. Because subsequent follow-up did not suggest rapidly progressing puberty, it is hypothesized that the estrogens may have arisen from the aromatization of adrenal androgens.

Though GH therapy has been linked to thelarche in prepubertal girls and to gynecomastia in boys [8, 9], the mechanism is not well understood. In our case, thelarche followed the onset of GH therapy, and as in the literature, GnRH-stimulated gonadotropin levels did not support activation of the pituitary–gonadal axis. It has been postulated that GH may act either directly on breast tissue receptors or indirectly through insulin-like growth factor 1 (IGF-1) to induce breast development [8]. A review of 68 girls with premature thelarche showed that they were significantly taller and had taller parents than controls, suggesting involvement of the GH–IGF-1 axis. Regression of breast

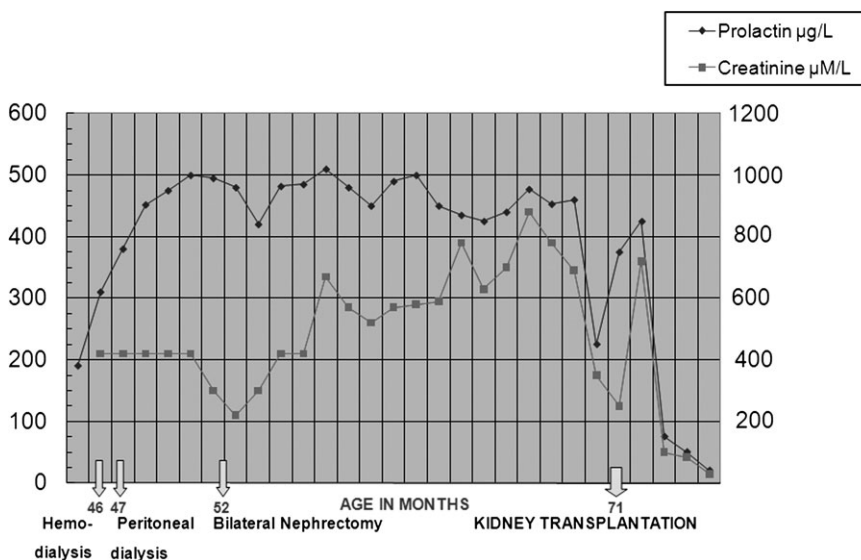


Fig. 1. Prolactin and creatinine levels 2 years prior to transplantation.

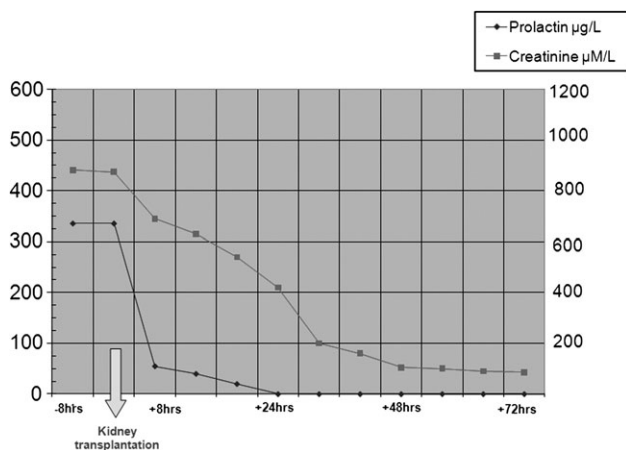


Fig. 2. Effect of kidney transplantation on serum prolactin levels.

development after withdrawal of GH therapy, as seen in our patient and reported in prepubertal girls after stopping 3 to 15 months of continuous GH replacement therapy [8], supports this hypothesis. PRL, though, does not seem to play a role in the genesis of premature thelarche [10]. In the case of our anephric patient, the observed moderate hyperprolactinemia in the presence of estrogen would likely have resulted in galactorrhea following GH-induced thelarche.

What is not fully understood is the precise mechanism whereby chronic renal failure leads to elevated serum PRL. In animals [11] and a number of uremic patients [12], both decreased clearance and increased secretion have been identified as potential causative factors. Under basal conditions, the kidney is the major pathway of PRL clearance; hepatic clearance of PRL has been estimated as only 10% that of renal [13]. Serum PRL levels would therefore be expected to rise if renal function were severely compromised [1]. Furthermore, serum PRL and creatinine levels are known to escalate in parallel as renal insufficiency progresses [12]. This is not surprising: PRL concentrations in human renal arterial and venous blood suggest a renal extraction rate of 16% [13], whereas the clearance rate of endogenous creatinine, generally taken as a measure of glomerular filtration rate, is roughly 20% of renal plasma flow. Thus, the clearance rates of PRL and creatinine by the kidney would be of similar magnitude, although to our knowledge, the renal clearance rate of PRL by glomerular filtration alone has never been reported.

In addition, it has been proposed that kidney parenchymal cells can break down PRL [14]. PRL is certainly reabsorbed by tubular cells, as are many polypeptides, and some of these molecules are degraded inside the cells. This hypothesis is supported by experiments in rats [11]. Uptake of PRL by tubular cells can occur from blood flowing in peritubular capillaries from the antiluminal pole of proximal tubular cells. The fact that PRL levels rose after BN in our patient who had previously had little or no kidney function would suggest that even uremic kidneys can eliminate PRL through tubular breakdown. Such a rise in PRL following BN has previously been reported [15].

It has been shown that chronic renal failure stimulates a dysregulation of PRL secretion, as evidenced by resistance

of lactotrophs to dopaminergic inhibition and by a blunted response to stimulation by thyrotropin-releasing hormone [16]. In the presence of uremia, bromocriptine was not very effective at inhibiting PRL secretion. It is believed that reduced kidney mass signals the hypothalamic/pituitary axis to promote PRL secretion; whether this occurs through removal of a negative or addition of a positive signal is not yet clear.

Plasma concentrations of parathyroid hormone and PRL are known to be linked [17]. However, in our patient, there was complete discordance between the two. Daily calcitriol doses, shown both *in vivo* and *in vitro* to promote PRL secretion [18], were also uncorrelated to fluctuations in PRL levels. Finally, stress has been shown to exert a minor effect on PRL levels [19], but it is doubtful that stress could have been an important factor in this case.

The striking feature in serum PRL levels in our patient was their very rapid decline following kidney transplantation. As PRL measurements in previous studies have been reported only weeks-to-months after transplantation, the time required to reach baseline has not been fully established [20, 21]. It has been suggested that normalization of PRL levels requires days if not weeks [3], implying some circulatory factor to be responsible for the delay in reduced production of PRL by lactotrophs. In our patient, however, PRL levels dropped to normal within ~8 h. Such a prompt response has never previously been reported. If one compares the elimination curve and time course between PRL and creatinine in serum, it is striking that creatinine took 3 days to normalize (Figure 2). Although PRL was not measured in the urine, it is tempting to surmise that the kidney was responsible for this efficacious elimination and that it was accomplished not only through glomerular filtration but also through tubular degradation [11]. The fact that renal plasma extraction of PRL has been reported to attain 29% [22], thus exceeding renal creatinine plasma extraction, would suggest that under certain circumstances, the kidneys are capable of clearing PRL at a faster rate than glomerular filtration would allow. It would further be surprising in view of the considerable accumulation of PRL in serum that a decrease in production by lactotrophs could significantly induce such a rapid change. We therefore conclude that in this child, renal elimination of PRL played a critical role both in the hyperprolactinemia following BN and in the accelerated return to reference range PRL levels following transplantation.

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*Conflict of interest statement.* None declared.

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