Complete regression of a major hyperprolactinaemia after renal transplantation

Hélène Bry-Gauillard1, Philippe Touraine1, Marie-France Mamzer-Bruneel2, Anna Simoes-Vaz1, Frédérique Kuttenn1 and Christophe Legendre3

1Department of Endocrinology and Reproductive Medicine, 2Department of Transplantation, Hopital Necker, and 3Department of Nephrology, Hopital Saint-Louis, Paris, France

Key words: chronic renal failure; dopamine resistance; hyperprolactinaemia; pituitary adenoma; prolactin; transplantation

Introduction

Macroprolactinomas do not seem to be more frequent in end-stage renal failure than in the general population. Nevertheless mild hyperprolactinaemia is common in patients with chronic renal failure (CRF). The prevalence of hyperprolactinaemia in CRF cases ranges between 20 and 75% [1–3]. In mild to moderate CRF, prolactin (PRL) levels are usually <100 ng/ml, although higher levels up to 2000 ng/ml have been reported in cases of hyperprolactinaemia secondary to drug intake. In patients undergoing dialysis, PRL levels are >100 ng/ml in 14% of cases, sometimes reaching 300–400 ng/ml [3]. After dialysis, PRL levels in such patients remain unchanged or slightly increased [4], whereas after renal transplantation, basal or stimulated PRL levels become perfectly normal [4–6]. The mechanisms leading to hyperprolactinaemia in CRF are unknown. One has to consider a decrease in PRL metabolic clearance rate (MCR) and/or disturbed hypothalamic regulation of PRL synthesis and release. The demonstration of impaired acute suppression by dopaminergic agonists supports the hypothesis of lactotroph dysregulation [5–7]. The response of prolactinomas to dopaminergic agonist therapy in patients undergoing haemodialysis and its evolution after transplantation could never be studied. We describe here the case of a patient with chronic renal failure and macroprolactinoma which was partially resistant to 15 mg/day bromocriptine before transplantation and became responsive thereafter.

Case

In October 1993, a 34-year-old Caucasian male with hyperprolactinaemia was hospitalized in the Department of Endocrinology.

Ten years previously, he had developed membranous glomerulopathy which progressed to end-stage renal failure requiring chronic haemodialysis in 1986. His adjuvant treatment combined 1.5 g/d calcium carbonate, 2 g/d aluminium hydroxide, 500 mg/d furosemide and 122 mg/d ferrous fumarate.

In October 1993, he complained of progressive impairment of visual acuity in the right eye, a sensation of breast tension without gynecomastia or galactorrhoea, and impairment of sexual potency. At admission, visual acuity was 6/10. The visual field showed exclusion of a blind spot. No sign of global pituitary deficiency or polyuria/polydipsy was observed.

Pituitary magnetic resonance imaging (MRI) showed a 3 × 3.5 × 3.5 cm tumour invading the right cavernous sinus and the chiasmatic cistern. The diagnosis of PRL-secreting pituitary macroadenoma was confirmed since the PRL level was 72 600 ng/ml (normal range <18 ng/ml). A blunted response to the thyreotropin (TRH) stimulation-test (increase of PRL <100% after 200 μg of TRH IV), was found together with a reduced testosterone level (1 ng/ml; normal range: 4–8 ng/ml), a normal estradiol level (10 pg/ml; normal range: 10–40 pg/ml), normal gonadotropins levels (LH = 5.5 IU/l; normal range: 2–12 IU/l, FSH = 4.65 IU/l; normal range: 2–12 IU/l) with a normal response to LHRH (LH = 5.5–20.6 IU/l, FSH = 4.65–7.4 IU/l), partial thyrotropin deficiency (T4 = 7 pg/ml; normal range: 9–16 pg/ml, T3 = 3.9 pg/ml; normal range: 2.4–5.3 pg/ml and TSH = 1.6 IU/l; normal range: 0.5–3 UI/l). Cortisol level was normal at 23.5 μg/dl, with a normal ACTH level at 61 pg/ml and a normal response to corticotropin releasing factor. GH secretion was normal. The final diagnosis was invasive PRL-secreting macroadenoma combined with partial gonadotropin and thyrotropin deficiency.

Treatment combined bromocriptine (from 2.5 to
15 mg/day), testosterone (250 mg/month IM) and L-thyroxine (100 μg/day). The patient’s visual acuity and sexual potency improved rapidly despite the persistence of hyperprolactinaemia. Indeed, PRL levels remained above 10 000 ng/ml. In June 1995, the PRL level was 25 200 ng/ml despite of 15 mg/day bromocriptine (Figure 1).

Pituitary MRI was performed every 4 months (the last before transplantation was made in June 1995) and showed no significant modification of the size of the adenoma.

In August 1995, the patient received a cadaver renal transplant. The immunosuppressive regimen combined azathioprine, corticosteroids (1 mg/kg solupred) and antithymoglobulin during the first 14 days, with cyclosporine A introduction at day 10. Dopamine (2.5 g/kg/min) was also infused continuously for 18 days. Improvement of renal function was delayed by acute tubular necrosis, and haemodialysis remained necessary for 8 days. Because of an acute rejection at day 20 post-transplantation, steroid treatment was increased. The patient was discharged on day 40 with serum creatinine at 178 μmol/l, which stabilized thereafter at around 140 μmol/l. The hormonal treatment remained unchanged throughout this period.

The day before transplantation, prolactinaemia was 8400 ng/ml. One week after transplantation, prolactin levels returned to normal range (4 ng/ml) under 15 mg/day of bromocriptine. One, 3, 6 and 9 months after transplantation, the patient’s PRL level was normal under the same treatment, thus confirming its stability (Figure 1). In November 1995 (4 months after transplantation), a new pituitary MRI showed that the tumour had shrunk from $3 \times 3.5 \times 3.5$ cm to $2.2 \times 3.0 \times 3.0$ cm with partial hemorrhagic necrosis; its involution continued on the last MRI performed in June 1996.

Four months after transplantation, thyrotropin function was normal without any L-thyroxine (L-T4 = 16 pg/ml; TSH = 0.52 IU/l). However, testosterone level remained low (1.3 ng/ml) without treatment and gonadotropins were in the low normal range, responding normally to LHRH (LH = 1.8–9.6 IU/l; FSH = 4.9–7.8 IU/l). GH secretion was normal.

**Discussion**

We report the case of a man with CRF and macroprolactinoma characterized by unusually high PRL (72 600 ng/ml). Whereas bromocriptine treatment was only partially effective during maintenance haemodialysis, PRL levels return to normal immediately after renal transplantation.

Before transplantation, we did not exclude that this patient had a macroadenoma, partially resistant to bromocriptine treatment, as it has been described in 10% of macroprolactinomas [8]. The patient received a maximal dose of 15 mg/day bromocriptine. The lack of improvement in PRL levels when bromocriptine was increased from 10 mg/day to 15 mg/day and the poor tolerance of high doses bromocriptine in this patient undergoing dialysis, did not press us to increase the bromocriptine dose. Nevertheless, the hypothesis of a molecular resistance to bromocriptine itself does not explain the dramatic decrease in PRL levels after

![Fig. 1. Evolution of prolactinaemia before and after renal transplantation.](image-url)
transplantation. We also performed a chromatography to ensure that the high levels of PRL were not false big-big PRL; we confirmed that the circulating PRL was the 23 kDa native PRL, as commonly described in CRF patients [2–4].

Prolactin normalization after transplantation might have been due to tumour infarction, promoted by haemodynamic changes during transplantation. No information exists concerning pituitary apoplexy during or after renal transplantation. Unfortunately, no immediate neuroradiologic imaging was carried out after transplantation. However, the absence of head-aches or ophthalmoplegia argues against spontaneous tumour infarction. Moreover, pituitary apoplexy is often complicated by GH deficiency reported in 88–100% of patients [9], which was not observed in our patient. However, we can not exclude this hypothesis. With regard to our patient, the pituitary MRI performed 4 months after transplantation showed partial haemorrhagic necrosis and mild tumour reduction which might have been a post-transplantation effect of bromocriptine.

To explain the patient’s functional resistance to dopaminergic agents, we would suggest renal failure as the main cause. The pathogenesis of uraemic hyperprolactinaemia is not understood clearly. It may be due in part to decreased PRL metabolic clearance rate (MCR), and also to the increase in PRL secretion caused by defective control of dopaminergic inhibition.

It is known that the kidney contributes to the MCR of low and medium molecular weight polypeptides, and that in renal failure, the levels of several circulating polypeptidic hormones rise [2], either by cessation of glomerular filtration or tubular reabsorption [10]. In humans, Sievertsen et al. observed a 33% decrease of PRL MCR in CRF patients compared with normal patients [2].

The other factor responsible is an increased PRL secretion due to a defect in dopaminergic inhibition [2]. Studies have demonstrated a threefold higher PRL secretory burst [2,11], a 33% higher burst frequency, a doubled PRL half-life and a calculated daily secretory rate 2.5 times higher in patients with CRF [11]. The PRL response after TRH stimulation [6] and the acute suppression by dopaminergic agonists [5–7] are reduced considerably. Many hypotheses are currently suggested to explain the lactotroph resistance to dopamine: the presence of a non-dialyzable factor in the serum of uremic patients which interferes with the dopamine binding to its pituitary receptor, the development of either a quantitative or qualitative alteration in the dopamine receptor, or alteration in the post-receptor metabolism of the prolactin. However, in CRF, molecular mechanisms of resistance to dopamine remain to be determined.

In conclusion, this case report underlines the changes existing in prolactin metabolism associated with CRF. We postulate that the partial bromocriptine resistance observed before transplantation was the consequence of the reduced PRL metabolic clearance and impaired lactotroph regulation by dopaminergic agonists induced by CRF. PRL normalization just after renal transplantation is most likely explained by the correction of the functional resistance to dopaminergic agents, possibly associated with partial tumour necrosis promoted by haemodynamic changes during transplantation.

References

Received for publication: 29.7.98
Accepted in revised form: 7.10.98