Transplantation of a Gitelman Syndrome kidney ameliorates hypertension.

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Abstract

Gitelman syndrome is caused by inactivating mutations of the gene that encodes the renal

sodium chloride co-transporter (NCC, SLC12A3) resulting in hypokalemia,

hypomagnesemia, hypocalciuria and a metabolic alkalosis. Renal salt-wasting commonly

provokes mild hypotension. The paucity of previous kidney transplants from donors with

known tubulopathies suggests that such conditions may be considered contraindications to

donation.

A 76-year old gentleman received a live unrelated kidney transplant from a donor with

known Gitelman syndrome secondary to a pathogenic mutation of *SLC12A3*. Immediate graft

function preceded emergence of the Gitelman syndrome biochemical phenotype and blood

pressure subsequently improved. The recipient developed unexpected hyponatremia.

Potential aetiologies are discussed, including the possibility that it paralleled the

physiological changes seen in the high volume state of thiazide-induced hyponatremia.

Transplanted kidneys are subject to nephrotoxicity from the use of calcineurin inhibitors.

Acquired Gitelman syndrome may confer a potential long-term advantage to the recipient

through both improved blood pressure control and also protection against the calcineurin

inhibitor-induced side-effect profile caused by NCC overactivation.

Both the donor and recipient remain well. In conclusion, Gitelman syndrome need not

preclude kidney donation and transference of the phenotype may have benefits for the

recipient.

Introduction

Gitelman syndrome is an autosomal recessive disorder caused by inactivating mutations of the gene that encodes the sodium chloride co-transporter (NCC, SLC12A3) located on the apical surface of distal convoluted tubular cells in the distal nephron. Those affected develop the biochemical phenotype of hypokalemia, hypomagnesemia, hypocalciuria and a metabolic alkalosis. Blood pressure tends to be low as a result of renal salt wasting. It is one of the commonest inherited tubular disorders with an estimated incidence of 1:40000[1].

Renal transplantation from donors with Gitelman syndrome has only been reported on two previous occasions[2,3] and in each case it was inadvertent. This suggests that tubulopathies, even with the usually mild phenotype of Gitelman syndrome, are considered a contraindication to donation by the transplant community. There is presently no guidance on the use of these organs for kidney donation.

However, rather than being detrimental, it is plausible that the presence of a salt-wasting tubulopathy like Gitelman syndrome in a donor organ may promote normotension and also mitigate against the adverse salt-retaining effects of calcineurin inhibitors (CNIs) which are mediated by increased NCC activity[4]; thereby conferring improved graft survival.

We report the planned transplant of a kidney from a living donor with Gitelman syndrome.

<u>Case report</u>

The recipient was a 76-year old man with end-stage renal disease due to histologically-proven hypertensive nephropathy who was maintained on peritoneal dialysis. Blood pressure control was sub-optimal despite triple anti-hypertensive therapy (once daily bisoprolol 5mg, amlodipine 10mg, doxazosin 4mg) with a blood pressure of 172/88 mmHg at the time of transplantation.

The donor was a 67-year old male, diagnosed with Gitelman syndrome 20 years earlier after incidental detection of asymptomatic hypokalemia. He had been prescribed amiloride 20mg twice daily to maintain a normal serum potassium concentration. His blood pressure prior to donation was 119/75 mmHg. He was genotyped using the TUBMASTR multiplex PCR platform [5] (Multiplicom, Santa Clara, CA) and was confirmed as being homozygous for a known pathogenic mutation of SLC12A3 (c.2221G>A; p.Gly741Arg). The donor was on no other medications and had no other significant medical history.

Laparoscopic left donor nephrectomy and implantation were uncomplicated. The recipient received the local standard immunosuppression protocol of basiliximab induction followed by maintenance therapy of tacrolimus, mycophenolate mofetil and prednisolone. The recipient's blood pressure, renal function, serum and urinary electrolytes were monitored in the post-operative period.

Immediate graft function resulted in a fall in serum creatinine to a baseline of 1.24-1.47 mg/dL (Supplementary Figure 1a). Serial serum and urinary electrolyte concentrations revealed transference of the Gitelman syndrome biochemical phenotype to the recipient.

Even though mild hypokalaemia was present from day 1, the potassium concentration did not fall below 3.0 mmEq/L and did not require supplementation (Supplementary Figure 1b).

Hypomagnesemia developed by day 7 post-transplantation (Supplementary Figure 1c). Persistent mild hypercalcemia (also evident in the donor) was apparent by day 19 (Supplementary Figure 1d), accompanied by hypocalciuria on both spot urinary calcium and 24-hour urinary calcium measurements.

A moderate hyponatremia developed (serum sodium concentration 124-131mEq/L) at day 10 (Figure 1a), associated with a decreased serum osmolality and an inappropriately high urine osmolality (254-400 mosm/L). This was initially coupled with a normal-high blood pressure (systolic BP 120-160mmHg), an ongoing diuresis (urine volume 3.5-6.4L/day), a naturesis (FE_{Na} 3.3%) and hypochloremia (Figure 1b). The serum urate concentration was low at 3.63 mg/dL. A random serum cortisol concentration was normal and there was no significant improvement with either oral sodium replacement or fludrocortisone treatment.

The recipient, who was hypertensive preoperatively, had no deterioration in his blood pressure post-transplant, despite treatment with tacrolimus and prednisolone. Indeed, his systolic, diastolic and mean arterial blood pressures all considerably improved, necessitating significant reduction of his antihypertensive medication dosage (bisoprolol reduced to 2.5mg OD, amlodipine reduced to 5mg OD) (Figure 2).

The post-operative period was also complicated by an episode of urinary retention requiring temporary re-insertion of a urinary catheter. The recipient also developed post-transplant diabetes mellitus, but did not require long-term insulin therapy. Graft function at one year was excellent (creatinine 1.19 mg/dL).

Twenty-four months post-transplant, the patient remains normotensive (128/78mmHg on the same antihypertensives). The characteristic Gitelman biochemical phenotype persists, weighing against the contribution of an ischaemic tubular insult. Chronic mild hypokalaemia (3.5mmol/L) with renal potassium wasting (FE_K 15.8%, spot urine,), and hypomagnesaemia

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(0.58mmol/L) with renal magnesium wasting (FE_{MG} 7.5%) remain. His serum sodium normalised (133mmol/L) with ongoing oral sodium chloride supplementation.

The donor had an uncomplicated post-operative course and remains well. Potential long-term risks specific to the donor by virtue of having Gitelman syndrome are minimal. His low-normal blood pressure and hypocalciuria will act to preserve his single kidney function from hypertension or nephrolithiasis. His renal function has remained stable since the time of donation.

Discussion

This planned transplant of a Gitelman syndrome live-donor kidney resulted in an excellent outcome despite the transfer of the classic Gitelman biochemical phenotype to the recipient.

Hypokalemia, hypomagnesemia, and hypocalciuria all developed in the first three weeks, a similar timeframe to the development of electrolyte abnormalities after starting a thiazide diuretic.

The development of hyponatremia was in the sameperiod. Only two cases of hyponatremia in patients with Gitelman syndrome have been published before; one associated with volume expansion, the other with hypovolemia[6]. Interestingly, the case previously reported by Hu *et al*. also received long-term sodium supplementation, probably for volume expansion [2]. It is tempting to ascribe hyponatremia in our patient to a low intravascular volume, with secondary ADH secretion causing free water retention and an inappropriately high urinary osmolality. However, the patient's hypertension, low serum urate concentration and unresponsiveness to sodium or mineralocorticoid weigh against this. Another possibility is that this was a phenomenon mimicking the high volume state seen in thiazide-induced hyponatremia. The timeframe (10 days) is similar to that reported for thiazide-induced hyponatremia[7], as is the hypochloraemia[8].The underlying mechanism of thiazide induced hyponatraemia is unclear, but recent evidence implicates prostaglandin E2 (PGE2)[8], which can increase collecting duct permeability to water independent of ADH. Increased urinary PGE2, which is usually associated with variants of Bartter syndrome, may also be raised in Gitelman syndrome[9]. PGE2 directly stimulates juxtaglomerular cells to release renin, and activate the renin-angiotensin-aldosterone system, causing many of the electrolyte abnormalities.

This raises the intriguing possibility that this hyponatremia might be responsive to non-steroidal anti-inflammatory drugs (NSAIDs). Indeed, NSAIDs are effective in ameliorating electrolyte abnormalities[10] and growth retardation[11] in Gitelman syndrome. There are currently no data concerning the use of NSAIDs in thiazide-induced hyponatremia, although indomethacin does decrease thiazide-induced PGE2 excretion[12]. Of course, NSAID administration post-transplant is likely to significantly decrease the GFR and produce gastric sequelae.

Our patient had a marked improvement in his blood pressure resulting in his antihypertensive requirement being halved. Hypertension is common post renal transplantation and is (in part at least) mediated by an increase of NCC activity caused by CNIs [4].

The hypertensive phenotype of tacrolimus (hypertension, hyperkalaemia, hypercalciuria and metabolic acidosis), closely resembles the phenotype of the Mendelian disorder Familial Hyperkalaemic Hypertension (caused by mutations of *WNK1*, *WNK4*, *CUL3* and *KLHL3*) and is due to overactivity of NCC. This is caused by dysregulation of its regulatory serine/threonine kinases, WNK1, 3, 4 and SPAK[4]. Furthermore, thiazide diuretics, pharmacological inhibitors of NCC, reverse tacrolimus-induced hypertension[4].

Given that Gitelman syndrome is the genetic equivalent of chronic thiazide diuretic administration (genetic and pharmacologic inhibition of NCC respectively) it is biologically plausible that transplanting a kidney from a donor with Gitelman syndrome will be beneficial for blood pressure control and, indeed, this is the experience of the two previously reported cases.

The incomplete resolution of hypertension in this patient may be explained by extra-renal elements of his pre-transplant hypertension as well as the systemic and renal vasoconstriction and reduced vasodilatation that may be caused by CNIs [13]. There is one report of the late

development of hypertension in patients with Gitelman syndrome[14]. It was speculated that this may be due to chronic activation of the renin-angiotensin-aldosterone system. As the donor is normotensive, this seems an unlikely explanation for the recipient's incomplete resolution of his hypertension; chronic hypertension is highly prevalent in transplant recipients[15].

Furthermore, the hypocalciuria transferred to the recipient may theoretically protect against CNI-induced osteopenia, which occurs in association with CNI-induced hypercalciuria[16]. Both Gitelman syndrome[17] and thiazide administration[18] are associated with increased bone mineral density. However, this effect may not be wholly due to renal calcium absorption; osteoblasts express NCC, and pharmacologic inhibition of NCC *in vitro* causes osteoblast differentiation, and mineralised nodule formation[19]. It may be that genetic inhibition of osteoblast, rather than renal, NCC function is the cause of increased BMD in Gitelman syndrome, in which case this theoretical advantage would not be conferred to the transplant recipient.

This case demonstrates that Gitelman syndrome need not preclude living donation and, indeed, may offer some advantages. It remains to be seen whether these theoretical advantages translate into better long term graft outcomes. Biochemical abnormalities may be transferred but can be anticipated and treated, as can volume expansion or depletion. Whether hyponatraemia is a frequent complication and what its aetiology is remain unanswered questions.

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Figure Legends:

Figure 1: Shows a) serum sodium over time b) serum chloride over time.

Figure 2: Shows a) the systolic and diastolic blood pressures and b) the mean arterial blood pressure over time with a best fit lines superimposed. Arrows indicate pharmacological interventions a) Bisoprolol reduced from 5 mg to 2.5 mg once daily b) amlodipine reduced from 10 mg to 5 mg once daily c) fludrocortisone 100 mcg once daily started.

Supplementary Figure 1: Shows serum electrolyte concentrations over time, with day 0 signifying the day of transplantation (dotted line), a) serum creatinine over time b) serum potassium over time c) serum magnesium over time and d) serum calcium over time.

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