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Nephrology
Dialysis
Transplantation

# *Letters*

## Conflict of Interest

Sir,
Given the intense pharmaceutical and often controversial involvement in the treatment of anaemia in chronic kidney disease, it is surprising that the authors of the reply letter [1] to the criticism of their paper [2] fail to declare the financial support they have received from the relevant companies when they made this declaration in their original publication some months earlier [3].

This omission raises the question of the value of voluntary compliance with conflict of interest declarations when authors fail to comply with the requirements of the conflict of interest form which is very clear, detailed and comprehensive in its format. The omission of conflict of interest declarations in industry sponsored supplements in *Nephrology, Dialysis Transplantation* is another example of the laxity employed in the observance of full compliance.

*Conflict of interest statement*. The author is a consultant for Fresenius Medical Care GmBH and Nipro Corporation, Japan.

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3. Locatelli F, Pisoni RL, Combe C *et al*. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004; 19: 121–132

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## Severe bladder dysfunction in a family with ADH receptor gene mutation responsible for X-linked nephrogenic diabetes insipidus

Sir,
We read with great interest the article by Shalev *et al*. [1] who reported a family affected by nephrogenic diabetes insipidus (DI) associated with hydroureteronephrosis and bladder dysfunction. The authors found a mutation of the aquaporin 2 gene (*AQP2*) to be responsible for the underlying concentration defect. As the authors indicate, the hyperdiuresis is thought to be responsible for the hypotonic large capacity-type bladders. We regularly see several patients affected by different forms of nephrogenic DI. We want to draw attention to one particular family with three boys affected by X-linked DI due to an R106C mutation in the *AVPR2* gene coding for the antidiuretic hormone (ADH) receptor. The maximal urine concentration capacity in these three patients is extremely reduced (140–215 mosm/kg) and diuresis ranges between 6 and 8 l/day. Ultrasound investigations revealed bilateral hydroureteronephrosis. Voiding cystography (VCUG) did not show any pathological reflux or outlet obstruction, but revealed an enlarged bladder (Table 1). Urinary flowmetry revealed a hypotonic large capacity-type neurogenic bladder similar to that described by Shalev *et al*. Clean intermittent catheterizations (CICs) are necessary in all three boys (Table 1). Undoubtedly the development of severe bladder distension in situations of extremely high amounts of hypo-osmotic urine remains rare. Nevertheless, our three patients presented with a bladder dysfunction of severity comparable with the cases reported by Shalev *et al*. Other authors have reported similar cases of bladder dysfunction in patients with nephrogenic DI [2,3]. *In vivo* studies in rats with hyperdiuresis evidenced a decrease in total bladder collagen content, but showed a normal contractile function [4]. It has not yet been elucidated if the large urine flow is the only contributing factor to the development of such urinary tract dilatation in DI. It is thought to exceed the capacity of the urinary tract, causing a functional obstruction and residual urine volume. One could hypothesize that severe distension of the bladder induces stretching of actin and myosin filaments responsible for the contractile defect in patients with severe bladder dysfunction. More complicated mechanisms might be involved in its pathogenesis, such as an independent associated urinary tract dysfunction. One could hypothesize that some gene mutations could be responsible for both the concentration defect and the bladder dysfunction in certain patients. These cases provide evidence that a similar phenotype is caused by two different gene mutations, which is a strong argument against a separate genetically mediated bladder dysfunction.

**Table 1.** Major clinical symptoms and results of radiological investigations in three male patients with a mutation of the ADH receptor gene responsible for nephrogenic DI

| Age | Nocturnal enuresis | Daytime enuresis | Need for CICs | Hydro/uretero nephrosis | Bladder volume (ml) in VCUG (SD) |
|---|---|---|---|---|---|
| 12 | + | + | + | + | 1000 (4.7) |
| 16 | + | – | + | + | 1200 (6.3) |
| 20 | + | – | + | + | 1200 (6.3) |

Bladder volume (mean ± SD) in healthy children >10 years old and adolescents measured by VCUG is 389 ± 129 ml [5].

In conclusion, a mutation of the ADH receptor gene can be responsible for DI with severe bladder dysfunction, as well as a mutation of the *AQP2* gene.

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## Hypercalcaemia from non-prescription vitamin A

Sir,
Use of over-the-counter 'natural' supplements may have unnatural effects. We report this case as a cautionary example.

A 67-year-old white man was admitted to hospital in late January 2004, with malaise and hypercalcaemia. He had undergone kidney transplantation 6 years earlier for kidney failure of unknown cause. Chronic allograft nephropathy occurred and the plasma creatinine rose to 400 μmol/l. He began to feel unwell in December 2003, and had a 5 kg weight loss. There was constipation, melena and haematochezia. His medications included prednisone, mycophenolate mofetil, atorvastatin, labetalol, bumetanide and potassium chloride. Blood tests showed a total plasma calcium of 4.2 mmol/l and he was admitted to hospital. On examination, there was a tremor and unsteadiness of gait. The plasma creatinine was 450 μmol/l. The ionized calcium level was 1.7 mmol/l (normal 1.2–1.3). Intravenous normal saline was given. Chest X-ray was normal. Upper and lower gastrointestinal endoscopy showed antral gastritis and two benign colonic polyps. Serum and urine protein electrophoresis did not show a paraprotein. The parathormone (PTH) level was 17 pg/ml, (normal 10–65) and that of PTH-related peptide was undetectable. The total plasma calcium reached 2.5 mmol/l by hospital day 4. On that day, further enquiry showed that he had been taking a dietary supplement containing vitamin A, on the advice of an eye doctor, for the possible diagnosis of macular degeneration. This over-the-counter supplement contains 7000 U of β-carotene per tablet and he had been taking four tablets daily since the autumn of 2003. Because of the possibility of vitamin A-induced hypercalcaemia, this supplement was stopped immediately. A retinol plasma level was 2550 μg/l (expected values 350–1200). A month later, he was feeling his usual self, the total plasma calcium had fallen to 2.4 mmol/l, and the plasma creatinine had fallen to 400 μmol/l.

The increasing use of dietary supplements and over-the-counter medicines, 'natural' or otherwise, may pose significant risks. In this case, the total daily dose of vitamin A that this patient was using was 28 000 U, whereas the recommended daily intake is only 5000 U. The association of vitamin A toxicity and hypercalcaemia is rare but well recognized. We found only eight case reports of this association in the past 30 years, the most recent being in 1988 [1].

The hypercalcaemia of vitamin A toxicity may occur because of activation of bone resorption by vitamin A [2]. This man's reduced baseline kidney function may have predisposed him to vitamin A toxicity. Given the modern prevalence of use of alternative medicines and supplements, more such cases may occur, which emphasizes the ongoing importance of vigilance and a careful medication history.

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## A fatal case of aluminium encephalopathy in a patient with severe chronic renal failure not on dialysis

Sir,
Aluminum (Al) toxicity in patients with end-stage renal disease is a well known adverse effect due to either dialysate Al contamination or oral intake of Al-containing phosphate binders [1]. At present, the clinical forms of Al toxicity have almost disappeared. Al-containing drugs are given mainly as antacid agents and are often used without special caution in patients with chronic renal failure (CRF) not yet on dialysis. Herein, we report a case of fatal Al-related encephalopathy in a patient with severe CRF, not on dialysis, due to the intake of large doses of antacids containing Al for at least 3 years.

*Case*. A 59-year-old white male patient with CRF due to diabetic nephropathy was followed as an out-patient in our chronic kidney disease clinic. When he was 47 years old, diabetes mellitus was diagnosed, and he was treated with oral antidiabetics for 2 years and thereafter with insulin. At 55, a severe polyneuropathy and distal occlusive arterial disease with foot gangrene occurred that required the amputation of the left foot. He suffered from gastric pain which he self-treated with Al hydroxide (Maalox® TC). A gastroduodenoscopy was performed that revealed antral gastritis positive for *Helicobacter pylori*. Despite the antibiotic treatment, the patient continued taking Al hydroxide. From the age of 57, he regularly attended our chronic kidney disease clinic. His serum creatinine was between 3 and 4 mg/dl