Adefovir-induced Fanconi syndrome: diagnostic pearls and perils of late or missed diagnosis

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Abstract Low-dose adefovir therapy has been increasingly recognised as a cause of Fanconi syndrome. Being relatively novel, early diagnosis is both fraught with difficulty and yet of paramount importance given its far-reaching consequences, many of which are amenable to treatment. We discuss a patient who presented with hypokalemia and other electrolyte abnormalities suggestive of Fanconi syndrome whilst on adefovir for hepatitis B. A trans-tubular potassium gradient (TTKG = 9.4) and urinary fractional phosphate excretion (39.4 %) consistent with renal potassium and phosphate wasting together with euglycemic glycosuria, aminoaciduria and hypophosphatemic osteomalacia supported the diagnosis of adefovir-induced Fanconi syndrome. With the cessation of the culprit drug, the patient has achieved partial recovery after 9 months. A high index of suspicion coupled with regular symptom surveillance and electrolyte monitoring is recommended in the course of adefovir therapy.

Keywords Adefovir · Fanconi syndrome · Hypokalemia · Hypophosphatemia · Osteomalacia

Abbreviations

ADV	Adefovir
PTH	Parathyroid hormone
HBV	Hepatitis B virus
FS	Fanconi syndrome
1,25(OH) ₂ D	1,25-Dihydroxyvitamin D
25(OH)D	25-Hydroxyvitamin D

Introduction

Adefovir (ADV) is an anti-viral drug used commonly at low doses for the treatment of hepatitis B viral (HBV) infection. Its use has been increasingly recognised to be associated with renal Fanconi syndrome (FS) [4].

Case presentation

A 62-year-old Chinese man was admitted to General Surgery for per-rectal bleeding from haemorrhoids, and referred to the Endocrinology service for hypokalemia (K 1.9 mEq/L) noted on routine investigations.

His medical history included smoking, well-controlled hypertension (on amlodipine 5 mg daily) and chronic HBV infection diagnosed in 2005 treated with adefovir diproxivil (ADV) 10 mg daily since 2007. His most recent liver ultrasound scan showed cirrhosis (Child's A) without splenomegaly or features of malignancy. His serum α -fetoprotein level was normal at 3 ng/mL (RI 0–9 ng/mL) and his HBV viral load was undetectable.

On systemic review, he had generalised myalgia, bone pain, loss of appetite and a weight loss of 10 kg over 6 months. He denied vomiting, changes in his bowel habit, haematuria, cough, consumption of alternative medicines or recreational substances. On physical examination, he was normotensive with no orthostasis. He was not cushingoid and had normal muscle strength.

In the work-up for his hypokalemia, a trans-tubular potassium gradient indicated a renal loss of potassium (TTKG = 9.4). This prompted further investigations (results and reference ranges listed in Table 1), which revealed a hyperchloremic normal anion gap metabolic acidosis and hypophosphatemia (PO₄ 0.4 mmol/L). His

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Table 1 Results of initial laboratory investigations

Investigations	Results	Reference interval
Sodium	141	134–144 mEq/L
Potassium	1.9	3.5–5.0 mEq/L
Urea	1.1	2.9–9.3 mEq/L
Creatinine	1.4 ^a	0.68–1.19 mg/dL
Creatinine clearance	53	mL/min
Albumin	3.7	3.5–4.8 g/dL
Adjusted calcium	2.24	2.15–2.58 mmol/L
Magnesium	1.1	0.7–1.0 mmol/L
Phosphate	0.4	0.8–1.6 mmol/L
Bicarbonate	15	19–31 mEq/L
Chloride	120	100–110 mEq/L
Anion gap	8	
Aldosterone	550	pmol/L
Renin	19.02	ng/mL/h
Aldosterone:renin ratio	28.92	pmol/L per ng/ml/h
24 h Urinary free cortisol	53	59–413 nmol/L
Free T4	10	8–21 pmol/L
TSH	1.09	0.34–5.60 mIU/L
PTH	13.3	0.8–6.8 pmol/L
FGF-23	62	<180 RU/mL
25-Hydroxyvitamin D	22	20–50 ng/mL
1,25-Dihydroxyvitamin D	16	18–64 pg/mL
C-telopeptide	0.485	0.154–0.885 µg/L
Osteocalcin	11	12–51 µg/L
ALP	349	38–126 U/L
Heat stable ALP	3 %	<20 % bone origin
Uric acid	2.59	4.20–9.25 mg/dL
24-h Urinary uric acid	467	84–975 mg/day

^a Normalised on repeat testing

urinary fractional excretion of phosphate was inappropriately raised at 39.4 % (normally <5 % in the presence of hypophosphatemia) [1], suggesting renal loss. In addition, the plotted renal phosphate threshold (TMPO₄/GFR 0.25 mmol/L, RI 0.89–1.34 for age and gender) was low (Fig. 1) [2]. He was also found to have secondary hyperaldosteronism along with euthyroidism and normocortisolism. Given his predisposition to hepatocellular carcinoma and weight loss, an assay for serum fibroblast growth factor-23 (FGF-23) was done which was normal (FGF-23 62 RU/mL), allaying concerns of possible oncogenic osteomalacia. Of the various non-FGF23-mediated causes of renal phosphate wasting [3], the patient was not using diuretics nor had he a history of childhood rickets, nephrolithiasis or features to suggest hypophosphatemic rickets with hypercalciuria (HHRH). He was normocalcemic (adjusted calcium 2.24 mmol/L) and had a raised intact parathyroid hormone level (PTH 13.3 pmol/L). Although his serum 25-hydroxyvitamin D level was normal

[25(OH)D 22 ng/mL], his 1,25-dihydroxyvitamin D level was low [1,25(OH)₂D 16 pg/mL].

Due to the presence of a normal anion gap metabolic acidosis and renal wasting of potassium and phosphate, we carried out a targeted evaluation for FS. A urine dipstick revealed a pH of 6.5, proteinuria and euglycemic glycosuria (serum glucose 112 mg/dL). His serum uric acid was low at 2.59 mg/dL with an inappropriately normal 24-h urinary uric acid of 467 mg/day. Urine amino acid quantification showed generalised aminoaciduria, in keeping with proximal tubular dysfunction.

As the patient was previously normokalemic (K 3.9 mEq/L in 2009), it was unlikely that his FS was inherited. Causes of acquired FS were actively excluded before ADV was determined to be the likely cause of the patient's tubulopathy.

ADV was stopped and the patient was switched to lamivudine for treatment of his chronic hepatitis B infection (he was unable to tolerate entecavir because of dyspepsia). Supportive measures implemented whilst waiting for tubular recovery included high-dose oral potassium (potassium chloride 1.8 g daily with a gradual tapering guided by serum levels) and phosphate supplementation (monobasic sodium phosphate 5 mL twice a day for 3 months). Cholecalciferol and calcitriol were initiated in the interim to normalise the elevated PTH levels from secondary hyperparathyroidism whilst awaiting recovery.

Table 2 shows the patient's investigation results after cessation of ADV in Sep 2012. Although our patient's biochemical abnormalities have yet to fully normalise, these trended towards recovery and he has been successfully weaned off phosphate and potassium supplementation and calcitriol. He has also reported significant improvement in symptoms, with reduced myalgia and bone pain, better appetite and some weight gain.

Discussion

The first report of ADV-associated hypophosphatemic osteomalacia was published in 2008 [4], with a number of reported cases of ADV-induced FS [5–12] since then. Most of the cases published were in East Asian subjects, which may either suggest a racial predilection, or an indication of the increased prevalence of hepatitis B infection requiring ADV treatment in East Asia.

ADV is used to treat chronic infections with HBV, a DNA virus utilising a reverse transcriptase for replication. ADV serves as a substrate for reverse transcriptase, resulting in chain termination. At doses of 30 mg daily for 48 weeks, ADV causes renal dysfunction in up to 13 % of patients [13]. However, large clinical studies have shown that at 10 mg daily, ADV shows little or no

Fig. 1 Nomogram for derivation of renal threshold phosphate concentration (reproduced with permission from Elsevier)

Table 2 Trend of investigation results after cessation of adefovir (stopped September 2012)

	Sep 12	Dec 12	Jan 13	Feb 13	Mar 13	Apr 13 ^a	Jul 13 ^b	Oct 13	Reference interval
K	1.9	2.8	2.9	3.8	3.7	3.4	3.4	3.8	3.5–5 mEq/L
PO ₄	0.3	0.3	0.4	1.5	1.1	0.6	0.8	1.0	0.8–1.6 mEq/L
ALP	211	242	349		308	272	236	204	38–126 U/L
Uric acid	2.59	2.69	2.54			2.40	2.99	2.90	4.20–9.25 mg/dL
HCO ₃	15	21	24				23	25	19–31 mEq/L
PTH	13.3	38.4		1.7	6.1	1.3	1.4	2.7	0.8–6.8 pmol/L
25-OH Vitamin D	22	24	15	18	26	34	45	45	20–50 ng/mL
Renin	19.02		21.76			24.72		8.44	—
Aldosterone	550		2367			937		482	—
Protein, urine dipstick	++		+			+	++	+	—
Glucose, urine dipstick	+++		+			++	++	—	—
Urine amino acids	Present		NA			Present			—

^a After cessation of phosphate replacement

^b After cessation of potassium replacement and calcitriol

evidence of nephrotoxicity after 48 weeks of treatment [14]. Nephrotoxicity associated with high-dose ADV typically has a late onset (>6 months) [15]. The time to onset of low-dose ADV-induced FS, based on case reports, ranges from a few months to >5 years [4–12]. In our patient, it took more than 2 years before the tubulopathy became apparent.

ADV-induced FS is postulated to result from the inhibition of DNA polymerase (required for mitochondrial DNA replication) after entrance into renal tubular cells through human renal organic anion transporter-1 (hOAT-1), causing adenosine triphosphate (ATP) depletion [16]. ATP depletion may then alter the activities of membrane transporters causing urinary solute loss. Features of FS thus

Fig. 2 Bone scan showing multiple insufficiency fractures. A bone mineral densitometry scan showed osteoporosis, and a bone scan showed multiple fragility fractures

include sodium wasting, polyuria and dehydration (with secondary hyperaldosteronism), metabolic acidosis, hypokalemia, hypophosphatemia and osteomalacia. These manifest as muscle weakness, fatigue, bone pain and pseudofractures. Such symptoms can be missed without a thorough systemic review.

In our patient, osteomalacia was diagnosed based on bone densitometry and radio-isotope scan results (Fig. 2) without histological confirmation from a bone biopsy. He likely had varying degrees of skeletal demineralisation and uncoupled bone remodelling based on the raised serum alkaline phosphatase associated with low levels of osteocalcin.

The effect of renal tubular dysfunction in osteomalacia causation appears to be multifactorial, with the primary mechanism relating to urinary phosphate wasting leading to deficient osteoid mineralization (phosphopaenic osteomalacia). The metabolic acidosis is also detrimental to bone mineralisation [17]. In addition, a reduction in 1-alpha-hydroxylase activity with low $1,25(\text{OH})_2\text{D}$ levels in FS is also proposed [18], resulting in metabolic bone disease through secondary hyperparathyroidism (which further increases urinary phosphate loss). All these in tandem result in a failure of bone mineralisation. Our patient's normal $25(\text{OH})\text{D}$ levels with low $1,25(\text{OH})_2\text{D}$ levels and raised PTH levels were consistent with decreased 1-alpha-hydroxylase activity. It is unlikely that vitamin D defi-

ciency was the cause of our patient's FS as that would require a much lower level of circulating vitamin D.

No randomised studies have been carried out thus far on the treatment of drug-induced FS. From the series of case reports so far, the time to resolution after cessation of ADV ranged from a few weeks to months [4–12]. A previous trial with high-dose ADV treatment showed a median time to resolution of renal dysfunction of 15 weeks, with the nephrotoxicity failing to resolve completely at 41 weeks after onset in 16 % of the patients [15]. In our case, complete biochemical recovery was not achieved at 1 year after cessation of ADV (Table 2). This case demonstrates that a degree of renal dysfunction may persist, which might even be irreversible, after cessation of the drug.

Conclusion

With the increasing number of reports of FS associated with low-dose ADV treatment, there may be a role for routine electrolyte monitoring to avoid the morbidity associated with missing this easily reversible condition. As FS may only become apparent several years into ADV therapy, we suggest a high index of suspicion and regular symptom review to guide the frequency of electrolyte monitoring. Time to biochemical recovery after ADV cessation may be protracted despite symptomatic relief.

Conflict of interest The authors have no duality of interest to disclose.

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