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BRIEF REPORT

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# Secondary renal Fanconi syndrome caused by valproate therapy

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**Abstract** Although renal Fanconi syndrome resulting from valproate (VPA) has occasionally been reported, the detailed clinical characteristics of this disease remain unclear. To clarify the clinical features of patients with VPA-induced Fanconi syndrome, we analyzed the clinical and laboratory data of seven affected patients. All patients were children, were severely disabled and required tube feeding. Five patients required treatment with multiple anticonvulsant agents. Hypophosphatemia and hypouricemia were found in all patients. Mild proteinuria, increased excretion of urinary $\beta$2-microglobulin ($\beta$2MG) and generalized hyperaminoaciduria were present in all patients. The renal biopsy of one patient exhibited tubulointerstitial nephritis without any structural abnormalities of the mitochondria in proximal renal tubular cells. All patients recovered from the Fanconi syndrome after the cessation of VPA therapy without any long-term renal sequellae. These results indicate that young age and being severely disabled with tube feeding and anticonvulsant polytherapy are contributory factors to the development of VPA-induced Fanconi syndrome. Serum phosphate and uric acid concentrations and urinary $\beta$2MG levels in addition to serum electrolytes and urinalysis should be examined regularly in patients receiving VPA therapy, especially in those with the contributory factors outlined above. Patients with Fanconi syndrome caused by VPA have a favorable renal outcome.

**Keywords** Valproic acid · Tubulointerstitial nephritis · Kidney disease · Epilepsy · Severe disability · Side effect

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## Introduction

Valproate (VPA) is a commonly used and effective antiepileptic drug for some patients with epilepsy. The side effects of VPA include gastrointestinal disturbances, elevation of hepatic enzymes, hyperammonemia, neurological disturbances, alopecia, weight gain, pancreatitis and thrombocytopenia [1]. Although renal side effects of VPA have occasionally been reported as Fanconi syndrome [2, 3, 4, 5, 6, 7], tubulo-interstitial nephritis (TIN) [8] or both [5, 9, 10, 11, 12], the detailed clinical and laboratory characteristics and precise pathogenic mechanisms remain unclear.

We have previously reported three severely disabled children with VPA-induced Fanconi syndrome [5, 12]. We have now encountered a further four patients with VPA-induced Fanconi syndrome. The aim of this study was to clarify the clinical characteristics of patients with secondary Fanconi syndrome caused by VPA.

## Patients and methods

The medical records of seven patients with secondary Fanconi syndrome due to VPA admitted to the Department of Pediatrics, Niigata City General Hospital, between 2000 and 2003 were retrospectively studied. Charts were reviewed for clinical characteristics, laboratory data, renal biopsy pathology and outcome. The complete type Fanconi syndrome was defined by generalized dysfunction of the proximal renal tubules leading to excessive urinary excretion of amino acids, glucose, phosphate, bicarbonate and protein [13]. Partial proximal renal tubular dysfunction resulting in excessive urinary excretion of some of these solutes was defined as an incomplete Fanconi syndrome [14].

## Results

Seven patients with VPA-induced Fanconi syndrome (five females and two males, aged 2 to 15 years, mean 7.7 years) were included in this study (Table 1). Patients numbered 5, 6 and 7 have been reported previously [5, 12]. Five patients exhibited a complete Fanconi syn-

**Table 1** Characteristics of patients with renal Fanconi syndrome due to VPA. *VPA* valproate, *CLB* clobazam, *ZNS* zonisamide, *DZP* diazepam, *CZP* clonazepam, *These three patients have been reported previously [5, 12]

| Patient no. | Age (years) | Sex | Underlying disorders | Duration of VPA therapy (years) | Opportunity that disclosed Fanconi syndrome | Severe disability | Tube feeding | Other anticonvulsants | Time until recovery (months) | Type of Fanconi syndrome |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 15 | M | Near drowning | 13 | Incidental laboratory studies | + | + | – | 3 | Incomplete |
| 2 | 6 | F | Neonatal asphyxia | 6 | Incidental laboratory studies | + | + | CLB | 2 | Complete |
| 3 | 6 | F | Neonatal asphyxia | 6 | Routine screening tests | + | + | – | 2 | Incomplete |
| 4 | 2 | F | Early infantile epileptic encephalopathy | 1 | Fever of unknown origin | + | + | ZNS, CLB | 3 | Complete |
| 5* | 4 | M | Pachygyria | 4 | Routine screening tests | + | + | DZP | 18 | Complete |
| 6* | 8 | F | Neonatal asphyxia | 8 | Incidental laboratory studies | + | + | ZNS, DZP | 2 | Complete |
| 7* | 13 | F | Neonatal asphyxia | 7 | Fever of unknown origin | + | + | CZP | 12 | Complete |

**Table 2** Blood laboratory data of patients with renal Fanconi syndrome due to VPA. *VPA* valproate, *Na* sodium, *K* potassium, *Cl* chloride, *P* phosphate, *BUN* blood urea nitrogen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase

| Patient no. | pH | $HCO_3$ (mmol/l) | Na (mEq/l) | K (mEq/l) | Cl (mEq/l) | P (mg/dl) | BUN (mg/dl) | Creatinine (mg/dl) | Urate (mg/dl) | AST (IU/l) | ALT (IU/l) | LDH (IU/l) | VPA (μg/ml) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 7.362 | 26.0 | 126 | 2.9 | 91 | 0.8 | 3.6 | 0.4 | 1.0 | 87 | 18 | 369 | 89.2 |
| 2 | 7.324 | 20.0 | 144 | 3.8 | 112 | 1.2 | 4.0 | 0.3 | 0.6 | 49 | 19 | 758 | 73.9 |
| 3 | 7.336 | 22.3 | 138 | 3.3 | 104 | 1.2 | 2.6 | 0.3 | 0.9 | 145 | 32 | 838 | 119.8 |
| 4 | 7.270 | 20.6 | 142 | 2.9 | 112 | 1.9 | 1.2 | 0.4 | 0.7 | 51 | 18 | 415 | 94.7 |
| 5 | 7.263 | 18.8 | 141 | 2.8 | 110 | 1.2 | 5.0 | 0.4 | 0.8 | 50 | 14 | 705 | 62.0 |
| 6 | 7.229 | 12.1 | 133 | 2.7 | 112 | 0.7 | 4.4 | 0.4 | 0.8 | 71 | 17 | 865 | 95.0 |
| 7 | 7.147 | 18.6 | 159 | 1.4 | 131 | 1.0 | 28.9 | 1.3 | 0.9 | 80 | 33 | 744 | 141.0 |

**Table 3** Urine and other laboratory data of patients with renal Fanconi syndrome due to VPA. *β2MG* β2-microglobulin, $FE_K$ fractional excretion of K, *n.d.*: not done, *%TRP* percent total reabsorption of phosphate, $FE_{UA}$ fractional excretion of uric acid

| Patient no. | Urinary protein (mg/dl) | Urinary β2MG (mg/l) | Urine glucose | Urine blood | Urine pH | Generalized aminoaciduria | $FE_K$ (%) | %TRP (%) | $FE_{UA}$ (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 56 | 76.45 | – | – | 8.0 | + | 8.4 | 78.0 | 28.3 |
| 2 | 17 | 17.24 | 2+ | – | 7.0 | + | 10.4 | 79.9 | 37.8 |
| 3 | 63 | 24.58 | 2+ | – | 7.0 | + | n.d. | n.d | n.d. |
| 4 | 24 | 48.22 | 1+ | – | 7.0 | + | n.d. | 65.5 | 52.6 |
| 5 | 36 | 47.02 | 2+ | – | 7.5 | + | 10.6 | 57.6 | 102.6 |
| 6 | 103 | 99.96 | 1+ | – | 7.5 | + | 21.6 | 18.1 | 62.3 |
| 7 | 88 | 56.29 | 2+ | – | 8.0 | + | 26.1 | 72.5 | 80.0 |

drome, while two patients had an incomplete Fanconi syndrome.

The underlying disorders were as follows: neonatal asphyxia (*n*=4), early infantile epileptic encephalopathy (*n*=1), pachygyria (*n*=1) and near drowning (*n*=1). All patients were severely disabled and required tube feeding. The development of Fanconi syndrome was revealed by incidental laboratory studies (*n*=3), by regular laboratory studies to detect adverse effects of VPA (*n*=2) and during the investigation of fever of unknown origin (*n*=2). The Fanconi syndrome developed 1–13 years (mean 6.4 years) after the initiation of VPA therapy. Two patients were treated with only VPA, while five patients required one or two additional anticonvulsant agents.

Laboratory studies (Table 2) revealed hypophosphatemia and hypouricemia in all patients. Hypokalemia, metabolic acidosis with a normal anion gap and hyponatremia affected six, five and two patients, respectively. One patient exhibited hypernatremia and hyperchloremia. The serum creatinine concentration was elevated in one patient. Serum VPA concentrations were above the normal therapeutic range in two patients. All patients exhibited elevated aspartate aminotransferase (AST) levels with normal alanine aminotransferase (ALT) levels.

Proteinuria, an increase of the urinary β2MG level and generalized hyperaminoaciduria were detected in all patients (Table 3). Glycosuria was detected in six patients. Decreased percent total reabsorption of phosphate (%TRP) and increased fractional excretion of uric acid ($FE_{UA}$) were found in six of six patients examined.

Only one patient (patient no. 7) underwent renal biopsy [12]. Light microscopy showed TIN with interstitial fibrosis. No glomerular abnormalities were found, and immunofluorescent studies did not reveal any depositions of imunoglobrins or complements. Electron microscopy showed no structural abnormalities of renal proximal tubular cell mitochondria [12]. All patients made a complete recovery from Fanconi syndrome 2 to 18 months (mean 5.6 months) after the discontinuation of VPA therapy without any renal sequellae.

## Discussion

Some patients undergoing VPA therapy exhibit subclinical renal tubular dysfunction. Novo et al. showed that 38.8% of the patients receiving VPA therapy exhibited increased levels of urinary N-acetyl-β-glucosaminidase (NAG), a proximal renal tubular lysosomal enzyme and a sensitive marker of proximal renal tubular dysfunction [15]. Korinthenberg et al. [16] demonstrated that urinary NAG levels were significantly increased in patients receiving VPA therapy as compared with healthy controls, and 20% of VPA-treated patients excreted more NAG than 95% of the control individuals. Altunbaşak et al. [17] reported that urinary NAG:creatinine ratios (NAG/Cr) were significantly higher in patients receiving VPA therapy compared to healthy controls, with 94% of patients receiving VPA therapy exhibiting a urinary NAG/Cr + 2 SD of control subjects. These studies indicate that proximal renal tubular dysfunction is more common in patients treated with VPA than had been previously believed. However, VPA-induced Fanconi syndrome is rare, and only 16 patients [2, 3, 4, 5, 6, 7, 9, 10, 11, 12] have been reported, including the 7 patients included in the present report. Among them, 13 patients showed no apparent extra-renal symptoms and were detected by screening laboratory tests or incidentally. It is our belief that increased attention to urinalysis or serum electrolyte levels in patients receiving VPA therapy will reveal more patients with Fanconi syndrome.

All patients in the present study demonstrated hypophosphatemia, hypouricemia, mild proteinuria, generalized hyperaminoaciduria and significantly increased excretion of urinary β2MG, while metabolic acidosis, hypokalemia and glycosuria were absent in some patients. Therefore, serum phosphate and uric acid concentrations and a urinary β2MG level should serve well as screening tests for the detection of VPA-induced Fanconi syndrome, and these should be examined regularly in patients receiving VPA therapy in addition to serum electrolyte tests and urinalysis.

The precise pathogenic mechanisms of Fanconi syndrome as a result of VPA remain unknown. Histological studies performed by Lenoir et al. and Hawkins et al. demonstrated mitochondrial abnormalities of renal proximal tubular cells in patients with VPA-induced Fanconi syndrome [2, 10] and suggested that VPA might directly injure mitochondria in proximal renal tubular cells. Because VPA has been reported to inhibit mitochondrial β-oxidation [10], VPA can contribute to mitochondrial dysfunction in proximal renal tubular cells. Interestingly, mitochondrial dysfunction may actually cause renal

Fanconi syndrome with the proximal renal tubular cells in congenital mitochondrial cytopathies exhibiting giant mitochondria [18]. However, as the renal biopsy of our patient did not exhibit any structural abnormalities of mitochondria in proximal renal tubular cells, there must be other pathogenic mechanisms underlying the development of VPA-induced Fanconi syndrome.

In the present study, all patients with VPA-induced Fanconi syndrome were severely disabled children requiring tube feeding. Five of seven patients received multiple anticonvulsant drugs. Previous reports have also shown that all affected patients were children with five of nine being severely disabled and requiring tube feeding and seven of nine receiving multiple anticonvulsant drugs [2, 3, 4, 6, 8, 9, 10, 11]. Although it is unclear why these factors predispose to the development of VPA-mediated renal injury, there are two potential explanations: an increase of serum toxic VPA metabolites in the serum and a decrease of serum carnitine levels.

VPA therapy may cause adverse effects other than renal injuries with hepatotoxicity being well known and developing in 15–30% of patients receiving VPA therapy [19]. This adverse effect is also likely to occur in children and patients receiving multiple anticonvulsant agents. Children have higher ratios of the concentration of toxic VPA metabolites to VPA. Polytherapy with enzyme inducers also increases the formation of the toxic VPA metabolites [19], which may induce mitochondrial dysfunction, resulting in renal injury as well as hepatic damage.

A decrease of serum total or free carnitine levels has been described in severely disabled patients receiving long-term tube feeding with carnitine deficient diets with [20] or without associated VPA therapy [21, 22]. VPA therapy itself can cause a deficiency of serum-free carnitine [23] because of the increased conversion of free carnitine to acylcarnitine and an increased urinary excretion of free and acylcarnitine [24]. Serum free carnitine plays a key role in the $\beta$-oxidation of fatty acids by facilitating their transport across the mitochondrial membrane [20]. Therefore, carnitine deficiency can cause mitochondrial dysfunction of proximal renal tubular cells. To confirm this hypothesis, serum carnitine levels should be examined in patients with VPA-induced Fanconi syndrome.

No patients developed chronic renal failure in the present study. Five patients recovered fully less than 4 months after the discontinuation of VPA therapy. Although two patients took more than 1 year to recover completely from Fanconi syndrome, the data suggest that patients with VPA-induced Fanconi syndrome have a favorable renal outcome.

In summary, young age, severe disability requiring tube feeding and anticonvulsant polytherapy are contributory factors to the development of Fanconi syndrome due to VPA. Serum phosphate and uric acid concentrations and urinary $\beta$2MG levels should be determined regularly in patients receiving VPA therapy in addition to serum electrolytes and urinalysis, especially in patients with the above contributory factors. Patients with Fanconi syndrome caused by VPA have a favorable renal outcome.

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