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Clinical Observations

Fever of Unknown Origin as the Initial Manifestation of Valproate-Induced Fanconi Syndrome

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ABSTRACT

BACKGROUND: Valproate-induced Fanconi syndrome is a rare adverse effect of valproate. Severely disabled patients who require tube feeding are reported to be susceptible to valproate-induced Fanconi syndrome. Although most patients with valproate-induced Fanconi syndrome are asymptomatic and detected incidentally with findings such as hypophosphatemia, hypouricemia, increased urinary β2-microglobulin, and generalized hyperaminoaciduria, clinical symptoms such as bone fracture, fever, tachypnea, and edema have been reported. **PATIENT DESCRIPTION:** This 15-year-old, severely disabled, tube-fed, male patient with cytochrome oxidase deficiency had taken valproate for 3 years when he developed fever for 3 weeks. Hypophosphatemia, hypouricemia, hypokalemia, increased urinary β2-microglobulin, and generalized hyperaminoaciduria, as well as hypocarnitinemia, were found, indicating that he had Fanconi syndrome. Valproate was the most likely cause of Fanconi syndrome in this patient. After discontinuation of valproate, the fever resolved immediately, and the laboratory findings normalized. **CONCLUSION:** Valproate-induced Fanconi syndrome should be considered when individuals taking valproate develop fever of unknown origin.

Keywords: Fanconi syndrome, valproate, fever of unknown origin, side effects, valproate-induced Fanconi syndrome

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Introduction

Fanconi syndrome is a generalized dysfunction of the proximal renal tubules that causes urinary excretion of amino acids, glucose, phosphate, bicarbonate, uric acid, and other substances. Valproate (VPA)-induced Fanconi syndrome is a rare adverse effect of VPA.[1] Several case reports have shown that severely disabled, tube-fed patients are vulnerable to VPA-induced Fanconi syndrome.[2,3] Most patients with VPA-induced Fanconi syndrome are diagnosed during routine or incidental laboratory examinations without any obvious symptoms.[2] The case of a severely disabled, tube-fed patient with cytochrome oxidase deficiency who presented with fever of unknown origin that was most likely caused by VPA-induced Fanconi syndrome is presented.

Patient Description

This 15-year-old boy was born at 41 weeks' gestation with a birth weight of 3270 g. His Apgar score was 3 at 1 minute and 6 at 5 minutes. He developed spastic tetraplegia and needed tube feeding. At age 4 months, he presented with infantile spasms. He was diagnosed with probable Leigh syndrome because of high lactate levels in the blood (39.6 mg/dL) and cerebrospinal fluid (34.5 mg/dL), as well as high-intensity signals in bilateral basal ganglia and thalami on T2-weighted magnetic resonance imaging at age 2 years. Pyruvate dehydrogenase complex activities in the lymphocytes and respiratory chain complex activities in the muscle, as well as histopathology of the skeletal muscle, were normal. Screening for known mitochondrial DNA mutations was negative. Seizure control was poor, and he had been on VPA and carbamazepine without l-carnitine supplementation from age 12 years. Two

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months before his admission at age 15 years, the VPA dose was increased (34 mg/kg/day) because of seizure deterioration, and l-carnitine (6 mg/kg/day) was added as a supplement to prevent secondary carnitine deficiency.

He was admitted to our hospital because of high-grade fever (39.1°C) that had lasted for 3 days. Bronchial pneumonia was suspected, and cefotaxime was administered. However, the fever persisted for 3 weeks. His body weight decreased from 16.7 kg at admission to 14.8 kg during the 3 weeks despite sufficient water (1800 mL/day) and caloric intake (1500 kcal/day). The following laboratory examinations were normal: white blood cell count, C-reactive protein, serological tests for viral or mycoplasma infection, antinuclear antibodies, rheumatoid factor, thyroid hormones, lymphocyte stimulation test for VPA, and bacterial and mycotic cultures. However, the erythrocyte sedimentation rate was high (90 mm/hr). Whole-body [F^{18}]-fluorodeoxyglucose positron emission tomography scan did not reveal any findings indicating focal inflammation. On the other hand, hypophosphatemia (1.3 mg/dL; normal 2.6-6.3 mg/dL), hypokalemia (3.3 mEq/L; normal 3.6-5.2 mEq/L), and hypouricemia (1.6 mg/dL; normal 2.0-7.0 mg/dL) were found, indicating the possibility of proximal renal tubular dysfunction. Urinalysis showed proteinuria, glycosuria, elevated β2-microglobulin (4460 μg/L; normal <230 μg/L), and generalized hyperaminoaciduria. These results confirmed Fanconi syndrome. In addition, hypocarnitinemia (19.0 μmol/L) was found despite carnitine supplementation, indicating secondary carnitine deficiency due either to VPA or Fanconi syndrome, or both. VPA was discontinued at 18 days from the start of fever. Four days later, the high fever resolved, and he gained 1 kg of weight. After the fever resolved, the l-carnitine supplement was increased (40 mg/kg/day) to treat hypocarnitinemia. Two months later, laboratory findings associated with Fanconi syndrome were normal. After recovery, a skin biopsy revealed cytochrome oxidase deficiency. The patient was not re-challenged with VPA, and no recurrence of Fanconi syndrome has been evident for more than 2 years.

Discussion

Fanconi syndrome is characterized by a general dysfunction of proximal renal tubules that causes urinary excretion of amino acids, glucose, phosphate, bicarbonate, uric acid, and other substances.[4] Recently, VPA-induced Fanconi syndrome has been recognized mostly in severely disabled patients.[2,3] The fever of unknown origin and weight loss in the present patient were likely the manifestations of VPA-induced Fanconi syndrome due to (1) the patient's vulnerability to this condition due to his diagnosis of cytochrome oxidase deficiency and severe disability requiring tube feeding, and (2) the fact that fever of unknown origin, weight loss, and laboratory findings indicative of Fanconi syndrome normalized after discontinuation of VPA.

A search of the PubMed database and the Japan Medical Abstract Society website for articles using the keywords "Fanconi syndrome" and "valproate" or "valproic acid" identified 20 reports of 49 patients (Table).[1-20] In these, sex and age were described in 37 patients (19 males and 18 females), with ages ranging from 2 to 32 years (median age, 8 years). As previously reported,[3] a high percentage of Japanese patients (36 of 49 patients) was evident. Among the 49 patients identified, 47 were described as being severely disabled (n = 42) or not (n = 5); in addition, feeding was described in 41 of the 49 patients, with 36 reported as being tube-fed. The duration of VPA treatment ranged from 3 months to 21 years (median, 4 years), and the VPA blood levels ranged from 21 to 141 μg/mL (median, 77.6 μg/mL). When VPA was discontinued, 45 of 47 patients recovered completely from VPA-induced Fanconi syndrome.

The duration needed for recovery ranged from 1 week to 18 months (median, 4 months). Two patients developed renal failure or continuing proteinuria despite the discontinuation of VPA.[6,13] Thus, the clinical course of VPA-induced Fanconi syndrome in the present patient was similar to the previous reports. Among the 13 patients in whom serum carnitine levels or carnitine supplementation was described, 3 patients had hypocarnitinemia,[11,16,19] 1 patient had a normal carnitine level,[15] and 9 patients with no description of serum carnitine levels had carnitine supplementation.[12,13,17,18] None of the patients whose serum carnitine levels were described had fever of unknown origin. Thus, there was no apparent association between hypocarnitinemia and prolonged fever, as appeared in the present patient. Furthermore, the weight loss and elevated erythrocyte sedimentation rate found in the present patient were not described in the other reported patients with VPA-induced Fanconi syndrome.

Overall, in 19 of the 49 reported patients, VPA-induced Fanconi syndrome was found on routine or incidental laboratory examinations without any obvious symptoms. In the remaining 30 patients, the initial clinical manifestations led to the diagnosis: 11 had fracture, 9 had fever, 3 had tachypnea, 2 had edema, 2 had weakness, 1 had anorexia, abdominal pain, and myopathy-like symptoms, 1 had hypertension, and 1 had fatigue and confusion. Among the 9 patients with fever,[8,9,14,15,20] 2 had prolonged fever described as fever of unknown origin.[8] In the remaining 7 patients, VPA-induced Fanconi syndrome was diagnosed and treated before the fever became prolonged.

In the present case, it took time to suspect VPA-induced Fanconi syndrome because fever is a common symptom in severely disabled patients. After infection was ruled out, more time was taken to rule out various other causes. The present case report, therefore, suggests the importance of considering VPA-induced Fanconi syndrome in severely disabled patients on VPA who develop prolonged fever and of measuring serum phosphate, uric acid, and electrolyte levels, as well as urinalysis including β2-microglobulin. The present case also suggested that supplementation with less than 10 mg/kg of carnitine is insufficient in these patients.

Although the precise pathogenic mechanism of VPA-induced Fanconi syndrome remains unknown, a mitochondrial abnormality in the proximal renal tubules is a typical finding of drug-induced Fanconi syndrome. There are at least three hypotheses for the pathogenesis of the renal tubular dysfunction. The first is an inhibition of β-oxidation in the mitochondria of the proximal renal tubules either directly by VPA or indirectly by the secondary carnitine deficiency caused by VPA.[1,5] The second is tubulo-interstitial nephritis (TIN) caused by hypersensitivity to VPA or a direct toxic effect of VPA.[5,8] The third is increased oxidative stress due to the VPA-induced decrease in plasma glutathione peroxidase activity, which causes mitochondrial dysfunction in the tubules.[1] The mechanisms of fever in VPA-induced Fanconi syndrome are unknown. Only two reported patients had prolonged fever of unknown origin, and TIN was found in one patient.[8] Because TIN can cause fever and weight loss,[8] fever of unknown origin and weight loss in the present patient might have been caused by TIN, but it could not be confirmed without renal biopsy. Another possibility is