Immunologically Mediated Chronic Tubulo-Interstitial Nephritis Caused by Valproate Therapy

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Dear Sir,

Valproic acid (VPA) is a highly effective drug for seizure disorders. It is well known that the side reactions of VPA are gastrointestinal upset, liver damage and thrombocytopenia, but only rarely are side effects seen in the kidney. Valproate therapy has been implicated as a cause of Fanconi syndrome in only two [1,2] and as a cause of acute tubulo-interstitial nephritis (TIN) in only one [3] previously reported cases. We encountered a patient with chronic TIN associated with valproate therapy, which was thought to be a seizure disorder for 18 months.

A 10-year-old boy with chronic TIN had apparently been well except for episodes of bronchial asthma and febrile convulsions, until the age of 10 years. He had an abnormal EEG at the age of 4 years and had been treated with VPA (300 mg/day; Kyowa Hakko Kogyo Co., Ltd. Tokyo) from the age of 8 years. Eighteen months after starting VPA therapy, glucosuria was noted on routine urinalysis. The patient was referred to another university hospital to examine glucosuria on February 5, 1989. Blood studies revealed a hemoglobin of 9.1 g/dl, a WBC count of 7,300/mm³, and a platelet count of 125,000/mm³. Liver function test results were within the normal range. Serum BUN, creatinine, and β_2 -microglobulin (β_2 -MG) were elevated to 30 (normal 8-17) mg/dl, 1.7 (0.6-1.2) mg/dl, and 6.6 (0.8-2.4) mg/l, respectively. Blood gas analysis showed metabolic acidosis with pH 7.25 and HCO₃⁻ 19.3 mEq/l. His urine had a pH of 5.7 with glucosuria(+), proteinuria(+) and generalized hyperaminoaciduria with normal concentrations of

plasma amino acids, but no cells or casts were present. Tubular functions were re-markedly deranged, as evidenced by the β_2 -MG index of 18.6 μ g/mg-Cr (< 0.4), N-acetyl- β -D-glucosaminidase index of 29.6 U/g-Cr (1.5-11.3), lysozyme of 9.4 μ g/ml (0), PSP test of 35% (120 min; 63-80), %TRP of 66% (85-98), FEHCO₃⁻ of 10.1% (< 3), and Fishberg test of 1.017 (> 1.024). His glomerular function was also decreased, as evidenced by a creatinine clearance of 38 ml/min/1.73 m² (120-140). From these results, he was diagnosed as having Fanconi syndrome and renal failure. On September 3, 1989, he was admitted to our department for further examination of the Fanconi syndrome and renal failure. On physical examination, his vital signs were stable and his growth was appropriate for age. He appeared slightly pale and his palpebral conjunctiva was anemic. The lungs were clear. A grade-1 systolic murmur was heard on the precordium. Abdominal examination was negative. No edema was found. Pigment degeneration

by metabolic disorders was not detected. The results of blood and urinary examinations performed on this admission revealed that tubular and glomerular function were lowered to same extent as in February. In the additional study of blood, serum globulins of IgG, IgM, and IgA were all within normal ranges, but IgE was elevated to 735 mg/dl (< 500 IU/ml). Serum complements were all within normal ranges and immunological antibodies of ANA, A-DNA-Ab, A-Sm-AB, and SS-A/SS-B were negative. The level of soluble CD4 (sCD4) was increased to 11.8 U/ml (control 6.4 ± 3.3), compared with an sCD8 level of 287 U/ml (control 371 ± 71) in the measurement of sCD4 and sCD8 in serum, which seems to correlate with T-cell subset activation. From these laboratory examination results with evidence of tubular and glomerular dysfunctions, he was suspected to have chronic TIN. To confirm the diagnosis of TIN, a renal biopsy was performed. Biopsy revealed the characteristics of chronic TIN with tubular disruptions, interstitial fibrosis, and infiltration of the interstitium with lymphocytes. A light microgram showed that the proximal tubules had architectural disruptions with focal cystic lesions, irregularities of epithelial cells and basement membranes. The interstitium had moderate fibrosis and marked infiltration of mononuclear cells. A marked fibrosis was recognized around the tubules and glomeruli. The distal tubules were relatively normal. The alterations in mesangium and basement membrane of glomeruli were not recognized (fig. 1). Immunofluorescence micrographs showed IgG and C3 deposited in sclerotic lesions of glomeruli and along the basement membrane of the proximal tubules in a linear pattern. Eighty percent of the filtrated T lymphocytes of the interstitium were CD4-positive cells, which were HLA-DR(+). A review of his medical history and laboratory data, indicating normal results of urinalysis and blood examinations before the beginning of VPA therapy, suggested that it was likely that his chronic TIN was caused by VPA. A skin patch test for VPA was positive, although a drug-induced lymphocyte-stimulating test was negative. It was investi-

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Fig. 1. Light microgram of biopsy specimen. Note the extensive infiltration of mononuclear cells into the interstitium and the marked fibrosis around the tubules and glomerulus. Disruptions of the tubular architecture with cystic dilatation, irregularities of epithelial cells and basement membranes were recognized in proximal tubules. Masson. $\times 175$.

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gated whether VPA could release cytokines as TNF- β or IL-2 from the peripheral lymphocytes of the patient, which could impair renal tissue. Release of TNF- β by stimulation of VPA (dilution rate 1:250) was significantly activated to 107 pg/ml, compared with 39 pg/ml in a control subject. The release of IL-2 was not activated to less than 0.8 U/ml, compared with 0.8 U/ml in a control subject. Hypersensitivity for VPA was present in this patient from the results of both skin patch test and release of TNF- β .

It is therefore likely that an immune-mediated case of acute TIN from hypersensitivity to VPA might become chronic if the primary process is not interrupted, although another possibility of idiopathic chronic TIN still remains.

Here we present a first case report of VPA-related chronic TIN. This was confirmed by the medical history and indirect evidence of immunological reactions for VPA, although direct evidence in renal tissue was not found.

References

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