Case 6

Delay of renal progression in methylmalonic acidemia by angiotensin II inhibition

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[Background]

Methylmalonic acidemia (MMA) is an autosomal recessive disorder of propionate, usually detected during the 1st year of life. MMA is caused by a defect of methylmalonyl-CoA mutase-apoenzyme activity or defective adenosylcobalamin (coenzyme) synthesis. Defect of the coenzyme may be treated with high pharmacological doses of hydroxocobalamin (B_{12}) with a consequent reduction in the production of methylmalonate and a less severe clinical course. Although infants with B_{12}-unresponsive forms are treated with low-protein diet, carnitine, and metronidazole therapy, these conservative therapies have not given optimal results in patients with vitamin B_{12}-unresponsive MMA until kidney or liver alone or combined transplantation.

The increasing numbers of children are surviving longer with appropriate treatment. As a result, longterm complications are becoming apparent. Classical methylmalonic acidemia is known to be associated with renal tubular dysfunction and chronic progressive loss of renal function due to progressive tubulointerstitial nephritis is frequent and a serious complication of long-term survivors with MMA. We report the considerable delay of chronic renal insufficiency caused by tubulointerstitial nephritis in a girl with MMA by angiotensin II inhibition.

[Cases]

This female patient presented with poor feeding and recurrent vomiting at 2 months of age. Her elder brother had also presented the same features and diagnosed as having MMA, however, died of sepsis at 9 months old. She was born uneventfully at term, with a birth weight of 2.9 kg. The diagnosis of MMA was established at the age of 2.5 months following systemic acidosis in the other hospital. Thereafter, she started a low-protein diet and treatment with carnitine and sodium bicarbonate. At age 3 years she presented choreoathetosis and, thereafter, permanent movement disorder remained, which showed abnormal signals in bilateral globus pallidus later. In that hospital, enzyme assays on fibroblast cultures were carried out, which disclosed that she had a defect in methlmalonyl CoA mutase with vitamin B_{12}-unresponsiveness. Although she has been sent to and treated at our hospital emergency room due to intermittent dehydration and acidosis with transient azotemia (plasma creatinine upto 2.1 mg/dL, 186 mol/L) and hyperkalemia, close observation and management have been done in previous general hospital.

From the age of 11.5 years she has been followed up through our out-patients clinics. At age 12 years enzyme assays on fibroblast cultures were carried out again in other hospital in USA, which disclosed the same results as before. At that time, the 24-hour creatinine clearance was 36.2 ml/min/1.73 m^2, and urine and serum MMA were 12.6 mM (2.4 mM/mM creatinine) and 1.5 mM, respectively. At age 14 years her blood urea nitrogen (BUN) was 21 mg/dL (7.5 mmol/L), plasma creatinine was 1.5 mg/dL (133 μmol/L), and serum uric acid concentration was 7.6 mg/dL (0.45 mmol/L). The 24-hour creatinine clearance was 30 ml/min/1.73 m^2. A renal ultrasound study revealed small-sized both kidneys considering her age. Following intermittent dehydration and acidosis, her plasma creatinine increased up to 1.9 mg/dL (168 μmol/L) especially at the age of 15.5 years, however, decreased to 1.7 mg/dL (150 μmol/L) by immediate management. However, her renal function decreased time by time after several

acute metabolic decompensations. Thereafter, we started angiotensin II inhibition by receptor antagonist, losartan, to hold renal progression with a close monitoring of serum potassium level. At the age of 17 years we performed a renal biopsy to see her renal pathologic status.

Despite of severe neurologic deficits including movement and speech problems she entered university with normal sensation and perception. At the age of 20 years she was placed on a continuous low-protein diet and received carnitine, sodium bicarbonate, and angiotensin II inhibitors of losartan (25 mg) and alacepril (12.5 mg) with her BUN 27 mg/dL (9.6 mmol/L), plasma creatinine 1.7 mg/dL (150 μmol/L), creatinine clearance 27 ml/min/1.73 m^2, serum uric acid concentration 7.9 mg/dL (0.47 mmol/L), and plasma potassium 5.0 mEq/L.

[Renal pathologic findings]

Light microscopic examination of seven glomeruli revealed three with near total global sclerosis; the remaining four showed normal looking appearance with equivocal mesangial cell proliferation. Focal patchy infiltrates of inflammatory cells were noted with interstitial fibrosis and tubular atrophy. Immunofluorescence study revealed no positive deposits.

[Points of discussion]

1. Renal outcomes of MMA.

2. Mode of renal progression in MMA?

3. Role of renal-angiotensin system in the renal progression of MMA.