

## A Case of Cystinuria with Nephrotic Syndrome<sup>\*)</sup>

Koji WADA, Naoki HAMAGUCHI, Misaki TADA,  
Michiko ARITA, Noriaki YORIOKA, Michio YAMAKIDO,  
Jyotaro HATA\* and Hisao ITO\*

*The 2nd Department of Internal Medicine, Hiroshima University School of Medicine,  
\*The 1st Department of Pathology, Hiroshima University School of Medicine, 1-2-3  
Kasumi, Minami-ku, Hiroshima 734, Japan*

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### ABSTRACT

The patient is 32-year-old, male who had been administered sodium bicarbonate and a small dose of  $\alpha$ -mercaptopyrionylglycine under the diagnosis of cystinuria, but during the 8th year of treatment he developed nephrotic syndrome. He suffered a number of recurrences which were treated each time with steroid only, but complete remission of nephrotic syndrome was achieved with the combined administration of methylprednisolone pulse therapy and cyclophosphamide.

### INTRODUCTION

Rosenberg et al.<sup>15)</sup> have reported that nephrotic syndrome in cystinuria is a renal disorder caused by treatment with D-penicillamine. Similarly the greater majority of cases with nephrotic syndrome in cystinuria have secondary nephrotic syndrome resulting from the administration of D-penicillamine. However, primary and secondary nephrotic syndrome due to  $\alpha$ -mercaptopyrionylglycine (MPG)<sup>12)</sup> in cystinuria are considered rare.

We recently experienced a case with cystinuria who subsequently developed non-drug induced primary nephrotic syndrome, although the possibility of it being a side effect of MPG cannot be completely negated. This case is introduced.

### CASE REPORT

The patient is a 32-year male with chief complaint of edema of the lower extremities. Past medical history includes surgery for median cervical fistula and appendectomy, but there has been no history of renal disease. Family history shows consanguineous marriage of parents.

Renal stones in the right kidney were pointed out in September 1970, and he underwent lith-

ctomy in November of the same year. In May 1972, he received surgery under the diagnosis of renal stones of the left kidney. At the same time, cystinuria was pointed out for which he was given a daily dose of MPG 300 mg and sodium bicarbonate. However, in 1974 and 1975 renal stones in the left kidney recurred for which he received surgery. He had been free of subjective symptoms until December 1980 when he suddenly developed edema of the face and legs, and was admitted to "S" hospital where he was diagnosed as nephrotic syndrome on the basis of severe proteinuria, hypoproteinemia and hypercholesterolemia, and treatment with a daily prednisolone dose of 40 mg was commenced. The dose of steroid therapy was gradually reduced, and as his condition improved and he was discharged from the hospital in February 1981. However, as his condition aggravated with the reduction of steroid dose, he was referred to our department for work-up.

Physical findings at time of initial examination showed height 161.6 cm, weight 47.5 kg, body temperature 36.6°C, pulse rate 74/min, blood pressure 136/86 mmHg and there were no abnormal findings of the heart or lung. On the

<sup>\*)</sup> 和田浩治, 浜口直樹, 多田みさき, 有田美智子, 頼岡徳在, 山木戸道郎, 幡城太郎, 井藤久雄: ネフローゼ症候群を合併したシスチン尿症の1例

other hand, steroid acne of the face, chest and back were observed, and operation scars were seen on the left and right lower abdomen. Edema of the face and legs were noted. Laboratory test findings showed proteinuria 1000 mg/dl, serum total protein 4.8 g/dl and serum total cholesterol 432 mg/dl, and as he had edema of the face and legs, administration of a daily dose of 40 mg of prednisolone was commenced. He was admitted to our ward two weeks later on August 5, 1981.

The laboratory findings at time of admission are as follows. Urinalysis showed a trace of albumin and 1/2% sugar, the sediment showed hyaline casts and cystine crystals. CBC revealed an increase in WBC to 14,000, but there were no abnormalities on coagulation tests nor liver function test. The total serum protein was 6.4 g/dl which is the lower limit of normal, and other findings included decrease in albumin, increase in  $\alpha_2$ -globulin, total cholesterol and triglyceride values. There were no abnormalities in the values of BUN, creatinine and uric acid, nor in serum minerals. Immunological tests showed a slightly decreased IgG and negative tuberculin reaction.

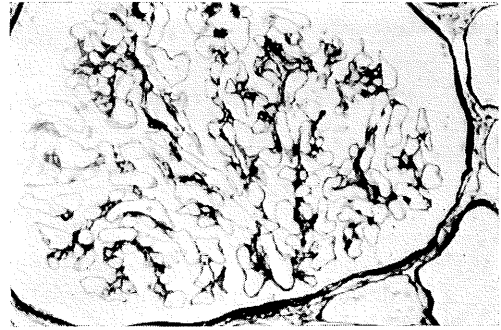
Intravenous pyelography showed dilatation of the left renal pelvis and renal calyx system due to renal stones and slight atrophy of the right kidney.

Renogram indicated a slight dysfunction of the right kidney, and renal scintigram also showed a slight atrophy of the right kidney, but there were no abnormalities in GFR, RBF, Ccr and PSP.

Plasma amino acid levels were normal for cystine, lysine, ornithine and arginine, but amino acid excretion in urine showed increases in cystine (486.2 nmol/ml), lysine (2726.2 nmol/ml), ornithine (828.3 nmol/ml) and arginine (1764.9 nmol/ml). The cystine oral load test failed to indicate an increase in cystine excretion into urine. The amino acid concentration in serum and urine samples from both parents showed a definite increase in urine cystine.

Histological findings showed slight proliferation of the mesangial matrix under light microscopy, but there was no thickening of the glomerular basement membrane (Fig. 1). Transmission electron microscopy showed slight foot process fusion, but no dense deposits were noted (Fig. 2). Scanning electron microscopy demon-

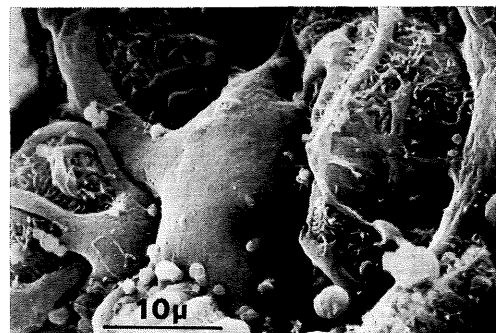
strated the presence of proliferation of microvilli on the surface of epithelial cell body and the processes (Fig. 3). Further, immunofluorescence microscopy was negative for IgG, IgA, IgM, C<sub>3</sub>, C<sub>4</sub>, and fibrinogen. On the basis of the above, this case was diagnosed as nephrotic



**Fig. 1.** Light microscopy shows slight mesangial proliferation, but there is no thickening of the glomerular basement membrane. (PAM)  $\times 200$



**Fig. 2.** Transmission electron microscopy shows slight foot process fusion without evidence of deposits.  $\times 12,000$



**Fig. 3.** Scanning electron microscopy demonstrates the presence of proliferation of microvilli on the surface of epithelial cell body and the processes.

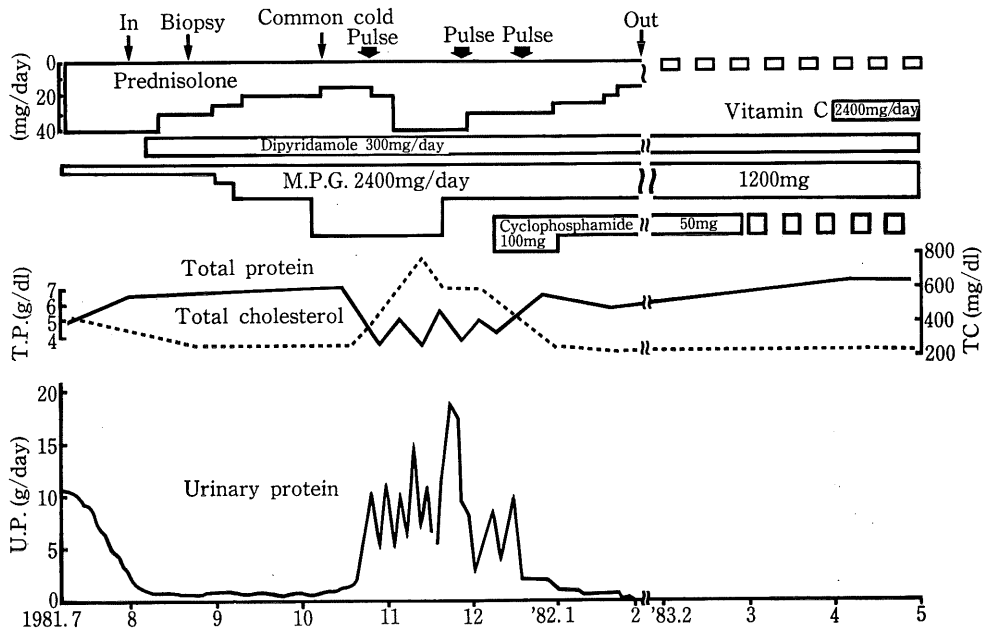


Fig. 4. The clinical course

syndrome with minimal change disease.

The clinical course is as shown in Fig. 4. The combination of prednisolone and dipyridamole was used for treatment and as the progress was good, the prednisolone dose was reduced from 40 mg to 15 mg, but as he caught cold at about this time, there was a marked increase in proteinuria. As it was considered a recurrence of nephrotic syndrome, two courses of methylprednisolone pulse therapy and after-treatment with prednisolone were administered. The proteinuria showed signs of decreasing, but as it increased again, one more course of methylprednisolone pulse therapy together with cyclophosphamide 100 mg/day were administered. Marked efficacy was achieved, and the prednisolone and cyclophosphamide doses were reduced. As there was no further recurrence, he was discharged in February 1982. Subsequently, the steroid dose was gradually decreased and complete remission was achieved.

On the other hand, treatment of cystinuria was commenced with the combination of sodium bicarbonate and MPG 300 mg/day, but as this proved ineffective, the dose was increased to 2400 mg/day. However, as gastrointestinal disorder developed, the dose was cut back to 1200 mg/day, and as no increase in renal stones has been seen, he is being continued on this

dose.

## DISCUSSION

Cystinuria is a hereditary disease characterized by the production of cystine stones due to increase in concentration of urine cystine. The cause for which are disturbance in reabsorption by the renal tubules and absorption by the intestine of cystine and such dibasic amino acids as lysine, arginine and ornithine, plus disruption of the transport of amino acids.

Cystinuria has been classified by Harris et al.<sup>6)</sup> in 1955 into two types, complete recessive type and incomplete recessive type. In 1966, Rosenberg et al.<sup>14)</sup> advocated the classification into 3 types based on cystine load test, incorporation of amino acids by the intestinal mucosa and amino acid excretion pattern. This classification is being widely used at present.

As our patient failed to show an increase in blood cystine concentration on oral load test, and as increases in urine cystine and lysine concentrations in his parents were noted, he is considered to be type II. Since Dent et al.<sup>4,5)</sup> reported that treatment of cystinuria should be directed at increasing urine output and alkalinization of urine, oral administration of sodium bicarbonate is being used. However, alkalinization of urine facilitates deposition of calcium

phosphate. This introduces the problem of increasing the size of the cystine stones by deposition of calcium. Thus, Crawhall et al.<sup>9)</sup> have advocated the oral administration of D-penicillamine as drug therapy for cystinuria. When administered orally, it forms a soluble cystine-penicillamine mixed disulfide, and as this disulfide is readily soluble, it prevents the formation of cystine stones. Subsequently, this drug has been widely used for cystinuria<sup>9,10)</sup>, but at the same it has a number of serious side effects<sup>7)</sup>.

The early side effects consist of rashes, joint pain, fever, swelling of lymph nodes, generalized fatigue and conjunctivitis, while those caused by long continuous use are proteinuria, membranous nephropathy, nephrotic syndrome, leukopenia, thrombocytopenia, eosinophilia, abnormal taste and inflammation of the optical nerve. Therefore, King<sup>8)</sup> and Thomas et al.<sup>18,19)</sup> advocated the use of MPG which has few side effects.

With regards to its dosage, Nishimura<sup>11)</sup> states that in order to maintain a cystine excretion of 200–300 mg/day, an MPG dosage of 1.5–1.6 g/day is necessary, but if alkaline therapy and large volumes of water are taken, 1.2 g/day would be sufficient. Araki et al.<sup>1)</sup> report that their goal for litholysis is to provide doses which would produce a urine cystine level of 100 mg/liter, and maintain it at 250 mg/liter for prevention of recurrence, but in practice it is necessary to consider the cystine excretion for each individual case and on the basis of this determine the MPG dose.

The side effects of MPG are practically nil when compared to D-penicillamine, but rarely serum sickness-like reactions such as rashes, fever, gastric disorder, generalized fatigue and swelling of lymph nodes develop. However, these are considered as a type of allergic reaction, and are said to disappear by discontinuing the use of the drug or carrying out hypo-sensitization therapy<sup>18,19)</sup>. Also renal disorder due to MPG is not totally non-existent, rarely such cases are reported. Stratta<sup>17)</sup> found 5 cases of nephrotic syndrome in liver disease patients being treated with MPG. Also Pavanello et al.<sup>12)</sup> reported 2 cases of childhood nephrotic syndrome which had developed as a complication to cystine being treated with MPG. In both cases, the patients were receiving large

doses (85–100 mg/kg/day) when the syndrome developed, but it disappeared by either discontinuing the drug or reducing the dose. As described above all cases with cystinuria complicated by nephrotic syndrome found by us were all secondary nephrotic syndrome cases induced by drugs.

We would like to review the developmental mechanism of nephrotic syndrome in our cystinuria case. The patient did receive sodium bicarbonate together with MPG, but the dose at the time of development of nephrotic syndrome was a small 300 mg/day, which makes it difficult to consider the occurrence to be a side effect of MPG. Further, if MPG as a chelating agent like D-penicillamine, caused renal tubulous disorder or membranous nephropathy, and induced the development of nephrotic syndrome, definite tubulous disorder and sub-epithelial dense deposits which suggest membranous nephropathy should be present, but there were no such findings in our case. Also as remission of nephrotic syndrome was attained while MPG was being administered, makes it difficult to consider MPG as the cause. Therefore, we find it difficult to believe that the nephrotic syndrome was a side effect of MPG.

Further, the possibility of the syndrome being caused by the repeated formation of renal stones which in turn frequently induced pyelonephritis can be considered, but this, too, can be ruled out from the histological findings. On the basis of the above, it is considered that this is a very rare case in whom primary nephrotic syndrome developed during the course of cystinuria, although the possibility of it being a side effect of MPG cannot be completely negated.

Very recently, Schmucki et al.<sup>16)</sup> and Brundig et al.<sup>2)</sup> have reported that large doses of vitamin C have proven to be not only effective for the treatment of cystinuria, but is also free of side effects. We are also trying its use.

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