A Case of Maple Sugar Urine Disease

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(Received for publication, November 18, 1962)

Maple sugar urine disease is an inborn error of metabolism, in which the symptoms such as feeding difficulty, weak crying or irregular, jerky respirations occur soon after birth, consequently growth failure is brought about and finally the death comes mostly due to a complication of bronchopneumonia within several weeks or months of life.1) Outstanding features of the disease are known to be a peculiar odor to urine resembling that of maple sugar and to be an excessive excretion of the three branched chain amino acids; leucine, isoleucine and valine in urine.1) Since the first description by Menkes et al.2) in 1954, a few cases have been reported in England and U.S.A.3-6) However, no report has appeared in Japan. In this paper, the first case of maple sugar urine disease in Japan will be reported.

CASE REPORT

Family history: The parents are healthy and not consanguineous. There is a brother who is living and well.

Past history: The patient, a female, was born, weighing 2.5 kg, with pelvic presentation after nine months' pregnancy and spontaneous delivery. She had a normal course of physiologic jaundice.

Present illness: Soon after birth, the patient was suffered from difficulty in feeding due to the development of dyspnea and vomiting on feeding. She was, therefore, forced to be fed with gavage but her body weight hardly increased. In addition, she had frequent episodes of fever of unknown origin. With the chief complaint of developmental retardation, the patient was admitted to our University Hospital at the age of 7 months.

Physical examination showed a poorly nourished girl in apparent distress. Her height was 60.5 cm, weight 5.1 kg and circumference of the head 40 cm; these values were remarkably low as compared with those of the normal; 66.2 cm, 7.52 kg and 42.5 cm, respectively. She could neither support her head nor sit alone.
yet. The crying was weak and the respirations were irregular associated with stridor. The pulse was regular with a good tension. She seemed to have no abnormality in vision or sensation. The bodily movements were inactive. The face was pale and somewhat cyanotic. The head was small but normal in configuration and the anterior fontanel was open about one fingerbreadth. The clear cardiac sounds were audible on the right side of the chest. There were dry rales heard over the right lung with no dullness to percussion. The abdomen was slightly distended. The liver was palpable two fingerbreadths below the costal margin but the spleen was not palpable. The extremities were rigid or at times flaccid and pes equinus was noticed. Neither clubbing nor cyanosis of the fingers was noted. All the deep tendon reflexes were intact. No pathological reflexes were elicited.

Laboratory findings: Examination of blood showed a hemoglobin of 12.5 g/100 ml, hematocrit 41%, R.B.C. 465 x 10⁴/mm³, and W.B.C. 10,500/mm³, with a differential count of 1% eosinophils, 30% lymphocytes, 7.5% monocytes and 61.5% neutrophils (no nuclear shift to the left). Erythrocyte sedimentation rate was 3 mm. in one hour and 12 mm. in two hours. Both the tuberculin and Wassermann reactions were negative.

Serum electrolytes were 141.0 mEq/l for sodium, 4.60 mEq/l for potassium, 4.25 mEq/l for calcium, 102.0 mEq/l for chloride and 4.15 mg/100 ml for phosphorus, respectively. Serum protein was 6.6 g/100 ml, nonprotein nitrogen in serum 28.0 mg/100 ml, and serum cholesterol was 175 mg/100 ml in total and 63 mg/100 ml in free form.

The liver function tests showed 0.5 unit for thymol turbidity test, 0.8 unit for zinc sulfate test, 1.0 B.L. unit for alkaline phosphatase, 60 units for SGOT and 45 units for SGPT.

The urine was straw-colored and clear with pH of 6.2, and contained no protein, sugar nor aceton. The urobilinogen excretion was within normal limits. The ferric chloride test for phenylpyruvic acid was negative. The sediments showed no abnormalities. The urine obtained on admission seemed to have no special odor but later a peculiar odor was noticed to the urine taken several days prior to the patient’s death. Stools were found to be free of ova and parasites and were negative for occult blood.

The funduscopic and laryngoscopic examinations revealed no abnormality. X-ray films of the chest exhibited an evidence of dextrocardia without enlargement of the cardiac shadow and a slight increase of the peribronchial markings over the hilar region. X-ray examination of the gastrointestinal tract revealed a free flow of the contrast meal through the esophagus into the stomach and the duodenum with no evidence of a hiatus hernia. EKG gave an almost normal tracing except the evidence of dextrocardia. EEG showed a diffuse dysrhythmia and the spike and sharp waves in the bilateral parietotemporal region (cf. Fig. 1).
Chromosomal analysis disclosed no abnormality in the number or configuration (cf. Fig. 2).

Summarizing the above laboratory findings, no definite diagnosis except dextrocardia and bronchitis was obtained, although more severe underlying disorder was suggestive from the clinical condition of the patient.

Course during hospitalization: Through the hospitalization, the patient had an irregular fever ranging from 35.2 to 39°C and frequent attacks of dyspnea and vomiting especially on her feeding. In spite of the forced feeding with gavage, the gain in weight was slow, indicating increase of 350 g for 45 days. On the 42nd hospital day, her condition was aggravated by the development of bronchopneumonia and 3 days later she died without effect of the treatment of antibiotics, corticosteroids, and so on.
Maple Sugar Urine Disease

Maple sugar urine disease 7 months +

Chromosome number 46

Fig. 2. Karyotype of chromosomes from our own patient with maple sugar urine disease.

Analysis of urinary amino acids: A 24-hour urine specimen, obtained a few days prior to the death of the patient when a peculiar odor to urine was noticed, was analysed for amino acids. The specimen was stored at -20°C until investigated. Analytical procedure of urinary amino acids was principally based on Ghadimi et al.'s method.5) Five ml of the urine specimen was passed through a column of Dowex 50 W–X8 (H+ form) and then amino acids adsorbed in the column were eluted with 2N NH₄OH. The eluate was gently evaporated to dryness over a water bath. It was reconstituted by an addition of 0.5 ml of water. An aliquot of 0.02 ml was spotted on a filter paper of Toyoroshi No. 50. Paperchromatography was carried out in two dimensions, using 80% phenol for the first direction and water-saturated n-butanol with the addition of glacial

Fig. 3. Paperchromatogram of urinary amino acids of the patient.
Key: 1. leucine & isoleucine, 2. methionine, 3. valine, 4. tyrosine, 5. alanine, 6. histidine, 7. lysine & arginine, 8. threonine, 9. glycine, 10. serine, 11. glutamic acid, 12. aspartic acid
acetic acid (water: n-butanol; glacial acetic acid=5: 4: 1 in volume) for the second direction. The spots of amino acids were stained by spraying with a 0.2% solution of ninhydrin in aceton.

The paperchromatogram of the patient's urine revealed an abnormal pattern of amino acids consisting of a remarkable increase in leucine, isoleucine, valine and methionine and an almost normal level of other amino acids (cf. Fig. 3).

Basing upon the clinical symptoms and the chromatographical findings of urinary amino acids as was described above, a diagnosis of maple sugar urine disease was established.

**DISCUSSION**

The primary lesion of maple sugar urine disease is supposed to lie probably in oxidative decarboxylation of the keto acids corresponding to the three branched chain amino acids\(^4\) (cf. Fig. 4), because \(\alpha\)-keto acids and \(\alpha\)-hydroxy acids corresponding to the respective three amino acids also are elevated in urine of the patients.\(^4,9,10\) It may be worthy of notice that methionine besides leucine, isoleucine and valine, was elevated in the urine from our own patient. Dent\(^1\) and Westall\(^8\) have found an elevation of methionine as well as three branched chain amino acids in plasma from the patient with this particular disorder. Methionine takes a quite different pathway in its degradation from the three branched chain amino acids (leucine, isoleucine and valine) which have a similar pathway in their degradation. Therefore, it is difficult to understand why methionine increases in this particular disorder. A possibility may exist that the keto acids or hydroxy acids elevated in the disease affect the metabolism of
methionine, resulting in an elevation of methionine in blood or urine. Dent et al.\textsuperscript{1)} have presented another hypothesis that a primary fault in this disease lies in an inability to convert methionine to cystine resulting in a diminished production of CoA and leading in turn to an accumulation of the branched chain keto acids (cf. Fig. 4). It remains to be solved that a primary defect lies either in the side of branched chain amino acids or in the side of methionine.

It is of interest to examine whether or not such a congenital metabolic disorder shows chromosomal anomaly. There has been no description on chromosomal analysis in the cases of maple sugar urine disease reported previously, while phenylketonuria has been demonstrated to have a normal pattern of chromosomes.\textsuperscript{11)} Our own patient with maple sugar urine disease was found to have no abnormality in chromosomes.

**SUMMARY**

A case of maple sugar urine disease, the first case in Japan, was described. The urine of the patient contained an elevated amounts of leucine, isoleucine, valine and methionine.

The chromosomal analysis gave no abnormality.

**Acknowledgment**

The authors are indebted to Dr. M. Ohira of Department of Dermatology, Faculty of Medicine, Tohoku University for chromosomal analysis.

**References**