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Case Report

MEVALONIC ACIDEMIA: FIRST CASE OF JAPAN

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Summary Mevalonic acidemia is a rare metabolic disorder due to mevalonate kinase deficiency which affects the biosynthesis of cholesterol and nonsterol isoprenes. We report the first case of Japan. The clinical course is characterized by intrauterine growth retardation, postnatal growth failure, intractable diarrhea, liver dysfunctions and death at three months of age. Dysmorphic features including triangular face, protrusion of forehead, hypertelorism, low set ears and micrognathism were noted. High mevalonic acid level was found by GC/MS.

Key Words mevalonic acidemia, mevalonic acid, mevalonate kinase deficiency, cholesterol biosynthesis, GC/MS

INTRODUCTION

Mevalonic acidemia is due to mevalonate kinase (MK) deficiency, the first enzyme after 3-hydroxy-3-methylglutaryl-coenzyme A reductase in the biosynthesis of cholesterol and nonsterol isoprenes. Very few patients with this disorder have been reported (de Klerk *et al.*, 1988; Gibson *et al.*, 1988; Kozich *et al.*, 1991; Hoffmann *et al.*, 1993; Mancini *et al.*, 1993).

The most severely affected patients have had profound developmental delay, dysmorphic features, cataracts, hepatosplenomegaly, lymphadenopathy, anemia,

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intractable diarrhea and malabsorption. Death in early infancy is common. Less severely affected patients have had psychomotor retardation, hypotonia, myopathy, and ataxia. They may have recurrent crises with fever, lymphadenopathy, hepatosplenomegaly, arthralgia, edema, and a morbilliform rash. Neuroradiological studies revealed atrophy of the cerebellum. Mevalonic acid concentrations were found to be grossly elevated in body fluids of all patients (Hoffmann *et al.*, 1993). Concentrations of plasma cholesterol are normal or only slightly decreased. Concentrations of ubiquinone-10 in plasma are decreased in most patients (Hübner *et al.*, 1993). This is the first report of mevalonic acidemia in Japan.

CLINICAL REPORT

Proband (II-5)

This male neonate was the second child of non-consanguinous healthy Japanese parents (Fig. 1). Three spontaneous abortions (II-2, 3, 4) were noted before his birth. His birth weight was 1,296 g at 34 weeks of gestation. Total cholesterol level in the early neonatal period was 42 mg/dl. At 3 months of age, intractable diarrhea appeared. After admission, dehydration, malnutrition and hypogammaglobulinemia were noted. He did not respond to treatment and expired after sudden cardiac arrest. Dysmorphic features including triangular face, protrusion of forehead, hypertelorism, low set ears, micrognathism and fragile hair (Fig. 2). Recurrent and intractable diarrhea, progressive hepatomegaly were noted. Later, we noticed that the clinical manifestations resembled those of mevalonic acidemia. Mevalonic acid level in plasma sampled at the first day of life was 407.2 ng/ml (about 100 times of normal level) by stable isotope dilution gas chromatography/mass spectroscopy (GC/MS: Nakura *et al.*, 1992). We could not study other chemical markers because available sample was not enough.

Case II-1

This female neonate is the deceased sister of the proband. Her birth weight was 1,600 g at 39 weeks of gestation. After birth, hypoglycemia, mild anemia, poor

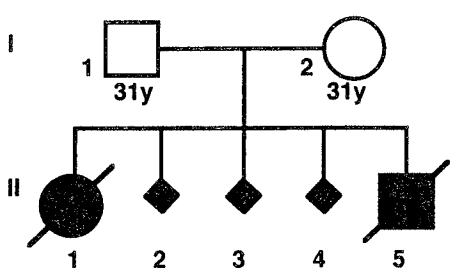

Fig. 1. Pedigree of the family.

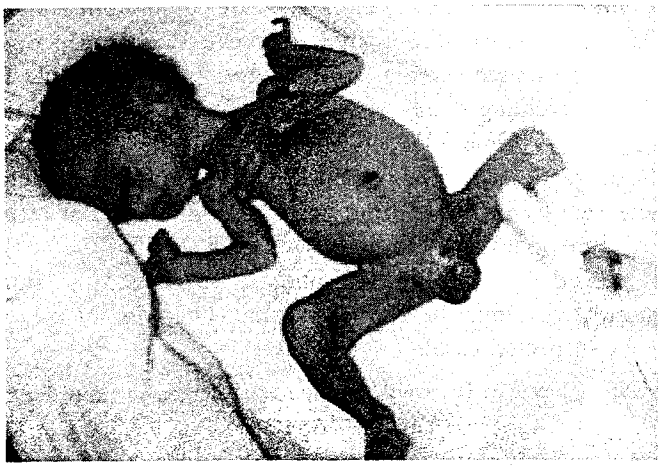

Fig. 2. General appearance of the proband.

weight gain and fever were noted. Elevation of transaminases were seen since 2 months (GOT 302, GPT 268 IU/liter). She weighed only 1,892 g at 3 months of age. Dysmorphic features were similar with those of the proband. Large fontanelle (3×3 cm) was noted. She was troubled by recurrent infections. She died of sudden cardiac arrest. Postmortem examinations revealed fibrotic change of liver with regeneration of lobules and focal fatty change. Neuropathological studies revealed cerebral polymicrogyria in the occipital area, decreased cerebral white matter and heterotopic Purkinje cells of cerebellum. Although chemical diagnosis of II-1 was not performed, her clinical course suggested the same disorder as the proband.

DISCUSSION

The clinical course and the dysmorphic features of the proband were similar with those of patients with mevalonic acidemia. Multiple miscarriages have also been observed in the families of mevalonic acidemia (Hoffmann *et al.*, 1993).

Schafer *et al.* (1992) isolated human MK cDNA clone and found a single base substitution (A to C) in the coding region at nucleotide 902 in the proband and the proband's father and brother, indicating that the patient was a compound heterozygote. This mutation changed an asparagine residue to a threonine residue (N301T). The N301T mutation is predicted to eliminate a β-turn of the MK protein and diminishes MK activity. But a disease-related mutation in DNA of the maternal allele of the proband and other patients have not been identified (Goebel-Schreiner *et al.*, 1995).

Deficiency of cholesterol biosynthesis may be the basic defect in this syndrome. Smith-Lemli-Opitz syndrome is also caused by a defect in cholesterol

biosynthesis (Tint *et al.*, 1994). CNS anomalies are common in Smith-Lemli-Opitz syndrome. Histopathological studies of II-1 revealed cerebral polymicrogyria in the occipital area, decreased cerebral white matter and heterotopic Purkinje cells of cerebellum. These changes may also be associated with defects in cholesterol biosynthesis in utero. Hübner *et al.* (1993) reported that MK deficiency leads to ubiquinone-10 deficiency which is responsible for the clinical progression of this disease characterized by increased lipid peroxidation, cerebellar atrophy, cataract development and myopathy.

We must consider mevalonic acidemia in neonates with similar features. Serum cholesterol levels may be low or normal. GC/MS for mevalonic acid is recommended in suspected cases.

REFERENCES

de Klerk JB, Duran M, Dorland L, Brouwers HA, Bruinvis L, Ketting D (1988): A patient with mevalonic aciduria presenting with hepatosplenomegaly, congenital anemia, thrombocytopenia and leukocytosis. J Inherited Metab Dis **11** Suppl 2: 233-236

Gibson KM, Hoffmann G, Nyhan WL, Sweetman L, Berger R, le Coultre R, Smit GP (1988): Mevalonate kinase deficiency in a child with cerebellar ataxia, hypotonia and mevalonic aciduria. Eur J Pediatr **148**: 250-252

Goebel-Schreiner B, Schreiner R, Hoffmann GF, Gibson KM (1995): Segregation of the N301T mutation in the family of the index patient with mevalonate kinase deficiency. J Inherited Metab Dis **18**: 197-200

Hoffmann GF, Charpentier C, Mayatepek E, Mancini J, Leichsenring M, Gibson KM, Divry P, Hrebicek M, Lehnert W, Sartor K, Trefz FK, Rating D, Bremer HJ, Nyhan WL (1993): Clinical and biochemical phenotype in 11 patients with mevalonic aciduria. Pediatrics **91**: 915-921

Hübner C, Hoffmann GF, Charpentier C, Gibson KM, Finckh B, Puhl H, Lehr H-A, Kohlschütter A (1993): Decreased plasma ubiquinone-10 concentration in patients with mevalonate kinase deficiency. Pediatr Res **34**: 129-133

Kozich V, Gibson KM, Zeman J, Nemecek J, Hoffman GF, Pehal F, Hyánek J, Grosmanová A, Verner P (1991): Mevalonic aciduria. J Inherited Metab Dis **14**: 265-266

Mancini J, Philip N, Chabrol B, Divry P, Rolland M-O, Pinsard N (1993): Mevalonic aciduria in 3 siblings: a new recognizable metabolic encephalopathy. Pediatr Neurol **9**: 243-246

Nakura K, Imada I, Sato K, Sakota K, Kawakami M (1992): An improved assay for mevalonic acid in blood. Igaku & Yakugaku **27**: 939-945 (in Japanese)

Schafer BL, Bishop RW, Kratunis VJ, Kalinowski SS, Mosley ST, Gibson KM, Tanaka RD (1992): Molecular cloning of human mevalonate kinase and identification of a missense mutation in the genetic disease mevalonic aciduria. J Biol Chem **267**: 13229-13238

Tint GS, Irons M, Elias ER, Batta AK, Frieden R, Chen TS, Salen G (1994): Defective cholesterol biosynthesis associated with the Smith-Lemli-Opitz syndrome. N Engl J Med **330**: 107-113