Biotin Responsive Multiple Carboxylase Deficiency Presenting as Diabetic Ketoacidosis

Jia-Woei Hou, MD, PhD

Multiple carboxylase deficiency (MCD) is a rare inherited metabolic disease of biotin dependency due to deficiency of holocarboxylase synthetase (HCS) or biotinidase deficiency. A 30-month-old female patient who presented with the initial features of diabetic ketoacidosis (severe metabolic acidosis, ketosis, and hyperglycemia), lactic acidemia, moderate hyperammonemia, and generalized organic aciduria is described. Associated symptoms and signs included erythematous skin rashes, alopecia and developmental delay. The patient responded dramatically to treatment with biotin (10 mg/day) showing normalization of clinical symptoms and most biochemical abnormalities. Based on the urine organic profile by gas chromatography/ mass spectrometry (GC/MS), the diagnosis of MCD was made. A plasma tandem mass study confirmed this diagnosis. The biotinase activity in serum was normal, indicating that this was a rare case of late-onset HCS deficiency. *(Chang Gung Med J 2004;27:129-33)*

Key words: diabetic ketoacidosis, biotin, multiple carboxylase deficiency, holocarboxylase synthetase.

Multiple carboxylase deficiency (MCD) are diseases of biotin dependency caused by holocarboxylase synthetase (HCS) deficiency or biotinidase deficiency.[1,2] They are autosomal-recessive type disorders of biotin metabolism, resulting in defects in fatty acid synthesis, gluconeogenesis and amino acid metabolism.[1,2] The clinical picture involves the skin, and the nervous, respiratory, digestive, and immune systems, but the great number of individual variations often makes the clinical diagnosis difficult.[1-4] Early diagnosis and appropriate treatment are essential in order to prevent death from metabolic acidosis or irreversible damage to the central nervous system.[2] Previously, researchers showed that HCS deficiency correlated with the early-onset form in most patients.[5,6] I herein report a case of late-onset of MCD with the initial presentation mimicking diabetic ketoacidosis (DKA).

CASE REPORT

A 30-month-old girl was referred for genetic analysis because of respiratory difficulty. She was the second child of healthy, non-consanguineous parents after an uneventful pregnancy and delivery with a birth weight of 3250 g. No metabolic disease or other genetic diseases were noted in the family. She was rather well except for mild developmental delay until this hospitalization. She developed the symptoms of poor appetite, vomiting, drowsiness, and tachypnea 5 days after one episode of respiratory tract infection, and was referred under the impression of having DKA. On admission, the patient was severely ill and had dyspnea with a respiratory rate of 60/min. Her body weight (BW) was 11 kg (10th percentile), body height (BH) was 82 cm (90th percentile), and head circumference (HC) was 47 cm

From the Division of Medical Genetics, Department of Pediatrics, Chang Gung Children's Hospital, Taipei.
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Address for reprints: Dr. Jia-Woei Hou, Division of Medical Genetics, Department of Pediatrics, Chang Gung Children's Hospital. 5-7, Fushing Street, Gueishan Shiang, Taoyuan, Taiwan 333, R.O.C. Tel.: 886-3-3281200 ext. 8203; Fax: 886-3-3278283; E-mail: houjw741@cgmh.org.tw

(10th percentile). Her skin was dry with eczematoid dermatitis over the periorbital and perioral areas. Her hair, eyebrows and eyelashes were sparse. The initial laboratory data showed hyperglycemia (592 mg/dL), metabolic acidosis (pH: 7.015 and base excess -31.1 mEq/L), mildly increased ammonia (151 μmol/L), lactic acidemia (12.2 mmol/L), and heavy ketonuria (4+) with ketonemia (0.25 mmol/L). Electrolytes were within the normal limits. Mild leukocytosis (15.0×10^9 cells/L) with normal differential counts, and normal liver and kidney function were also noted. Fundoscope examination results were normal. Type 1 DM was excluded by normal C-peptide levels after the glucagon test. The urine organic acid profile detected by gas chromatography/mass spectrometry (GC/MS) study showed markedly elevated 3-OH-isovaleric acid, 3-methylcrotonylglycine, mildly increased lactic acid, 3-OH-propionic acid, 3-OH-n-butyric acid and the presence of tiglyglycine and methylcitric acids (Fig. 1A). The pattern was typical of MCD as a result of either HCS or biotinidase deficiency. The metabolic profile (pH value, glucose, and ammonia) was recovered soon after intravenous fluid rehydration, diet control with protein restriction 1.5 g/kg/day and treatment with 10 mg of biotin per day. The abnormal organic acids were markedly decreased (Fig. 1B). Plasma amino acids showed slightly increased glycine and alanine levels. Normal biotinidase activity was noted (Neogene Screening Inc. Pittsburgh Penn, USA). Acylcarnitine profile of the blood sample via tandem mass showed elevated propionylcarnitine and 3-OH-isovalerylcarnitine which were consistent with MCD. The follow-up data were normal.

The patient had mild retardation in neuro-development and growth during the first 2 years of life, and she has been enrolled in a rehabilitation program. Biotin was administered continuously. On follow-up examination, the patient was doing better in motor and speech abilities. At the age of 4 years, her BW, BH and HC were all at 50th percentile of the growth chart.

DISCUSSION

A case of late-onset HCS deficiency presenting with DKA was described. The symptoms and signs of DKA and abnormal metabolic profile responded dramatically to a short trial of biotin without recurrence. Before biotin treatment, the pattern of urinary organic acids showed levels of highly elevated 3-hydroxyisovaleric acid and 3-methylcrotonylglycine, mildly increased lactic and 3-hydroxypropionic acids, and modest elevations of methylcitric acid and

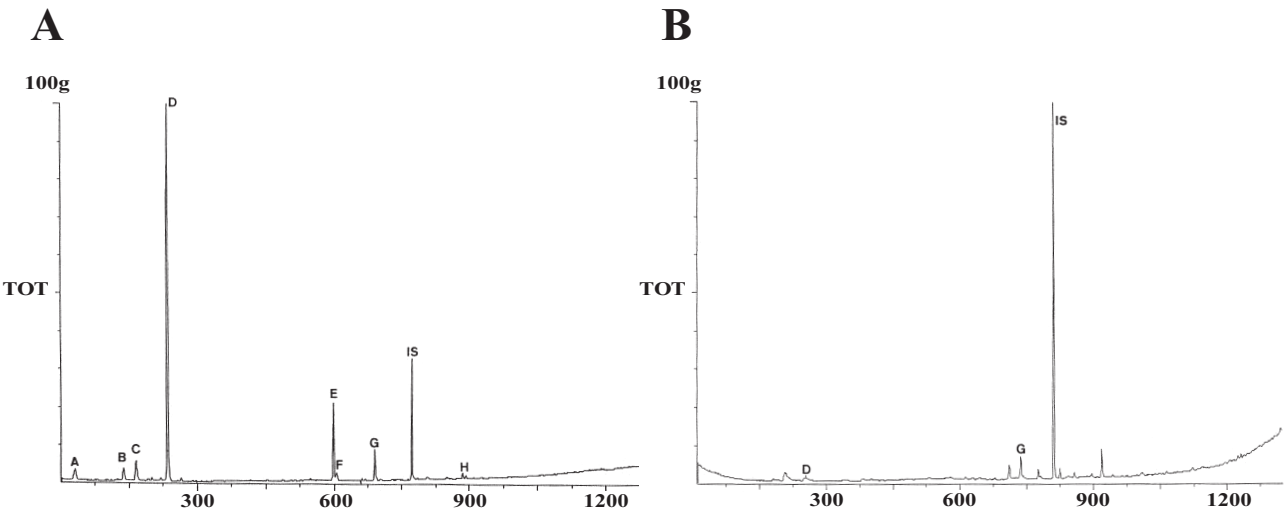

Fig. 1 **[A]** The urine organic acid profile detected by GC/MS study shows mildly increased lactic (A), 3-OH-propionic (B), 3-OH-n-butyric (C) acids; and markedly elevated 3-OH-isovaleric acid (D), 3-methylcrotonylglycine (E), and the presence of tiglyglycine (F) and methylcitric acid (H), (G) 4-OH-phenylacetic acid; (IS) internal standard. **[B]** After treatment with biotin for 3 days, the abnormal organic acids are markedly decreased.

tiglylglycine (Fig. 1A), which were typical of MCD.[7,8] The elevated organic acids decreased or normalized after starting biotin treatment (Fig. 1B). A late-onset and biotin-responsive case of HCS deficiency was thus confirmed in this patient according to normal biotinidase activity, the typical findings of both GC/MS and tandem mass studies.

Biotin is a water-soluble vitamin found in all organisms and functions as a cofactor of enzymes known as biotin-dependent carboxylases. HCS is an enzyme that catalyzes the covalent attachment of biotin to five biotin-dependent carboxylases in human cells.[1,3] In humans, there are three mitochondrial carboxylases, namely, pyruvate carboxylase, propionyl-CoA carboxylase, and methylcrotonyl-CoA carboxylase. MCD is a life-threatening disease characterized by the lack of carboxylase activities because of deficiency of HCS activity.[1] Only few cases of deficiency of HCS have been reported since 1993.[4-6, 9] Most patients with HCS deficiency have shown acute episodes of metabolic acidosis and characteristic organic aciduria due to the decreased activity of multiple carboxylases before they are a few months old.[1-3] Symptoms include tachypnea, feeding difficulties, seizures, and even coma or death. Biotin-responsive MCD may present in an early-onset or late-onset form.[1-3] The former is initially caused by HCS deficiency, and the latter by biotinidae deficiency. Only some patients with HCS deficiency became symptomatic later during the infantile period.[5,6] They are considered to be of a milder form of HCS deficiency.

Biotinidase deficiency (late-onset MCD) results in reduced activities of the four biotin-dependent carboxylases. Patients with biotinidase deficiency show similar but more severe features than those with HCS deficiency such as skin rashes, alopecia, kerato-conjunctivitis, hypotonia, psychomotor retardation, ataxia, progressive deafness, seizure and life-threatening episodes of metabolic acidosis.[1] This disease is generally fatal without treatment and survivors suffer from severe neurological damage.[1-3]

Generally speaking, the clinical presentation and age of onset of each condition are extremely variable. This patient may have had a mild form of HCS deficiency, however DKA with mild hyperammonemia was the first presentation. A few metabolic diseases such as branched chain aminoacidopathy and organic acidemias (methylmalonic, isovaleric and propionic acidemias) may also present with DKA.[1-3,10,11] Metabolic evaluation enabled the differentiation of those conditions. HCS is usually a treatable metabolic disorder masquerading as cerebral palsy. Congenital disorders with MCD respond clinically and biochemically to oral biotin therapy. The prognosis of MCD is good when biotin is introduced early and continued through life.[1-5]

The underlying mechanism in HCS deficiency, discovered in 1981, is the decreased affinity of HCS for biotin which impairs the formation of HC at physiological biotin levels.[2] The human HCS cDNA has been isolated and shown to encode 726 amino acids.[12] The primary defect of mutant HCS had been believed to be a deficient HCS activity or the Km for biotin is elevated leading to decreased affinity for biotin.[1-3] In a pregnancy at risk for deficiency of HCS, prenatal diagnosis was performed by assay of the enzyme in amniocytes.[5] Mutational analysis of the HCS gene was possible only in some families because the spectrum of reported mutations of the human HCS gene varied substantially among different ethnic groups.[13-15] Prenatal treatment of the mother as early as possible with biotin led to a good outcome for the infant at birth.[5,9] Newborn screening by the tandem mass also offers the opportunity for early diagnosis and treatment of the disease in the general population.[16]

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以糖尿病酮酸中毒表現之生物素反應性多脫羧酶缺乏症

侯家瑋

多脫羧酶缺乏症爲一罕見，生物素依賴型的先天代謝疾病，它可因全脫羧酶合成酶或生物素酶缺少引起。前者多爲早發型，後者則爲晚發型。本報告爲一位二歲半女孩以糖尿病酮酸中毒爲主要表現，包括嚴重代謝性酸血症、高酮血症、高血糖、高乳酸血症、高血氨症、及有機酸尿症。以高劑量生物素 (10毫克/ 天) 治療後病人症狀及實驗室變化已有明顯改善，其他慢性症狀只有發展遲緩，皮疹及毛髮較少。經由尿液有機酸氣相光譜質譜儀變化及血液串聯質譜儀均符合多脫羧酶缺乏症。由於本病人之生物素酶活性爲正常，因此可能是較少見的晚發型全脫羧酶合成酶缺乏症。(長庚醫誌 2004;27:129-33)

關鍵字: 糖尿病酮酸中毒，生物素，多脫羧酶缺乏症，全脫羧酶合成酶。

長庚兒童醫院 台北院區 兒童內科部
受文日期：民國92年4月9日；接受刊載：民國92年6月2日。
索取抽印本處：侯家瑋醫師，長庚兒童醫院 兒童內科部。桃園縣333龜山鄉復興街5-7號。Tel.: (03)3281200轉8203; Fax: (03) 3278283; E-mail: houjw741@cgmh.org.tw