Growth Hormone Therapy in Neonatal Patients With Methylmalonic Acidemia

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Background: Information regarding growth hormone (GH) therapy in neonatal patients with methylmalonic acidemia (MMA) is lacking. We present our experience with GH therapy in neonatal patients with MMA.

Methods: Four neonatal patients with *mut*^{0} type MMA were identified through newborn screening for elevated propionylcarnitine (C3) levels. GH therapy (0.6 IU/kg/week, subcutaneously) was prescribed for patient 1 after 1 month of admission, and was prescribed for patients 2, 3 and 4 on the 1st day of admission. We evaluated weight, skin erosion, hospital stay, and serum levels of C3 after GH therapy.

Results: All of the neonatal patients with MMA displayed obvious weight gain and distinct improvement in skin erosions after GH therapy. The duration of hospital stay for patients 2, 3 and 4 was reduced compared to that of patient 1. However, the metabolic effects of GH therapy on reducing serum levels of C3 seem to be indeterminate.

Conclusion: Our clinical findings suggest that GH therapy has potentially beneficial effects on neonatal patients with MMA. [*J Chin Med Assoc* 2009;72(9):462–467]

Key Words: C3, growth hormone, methylmalonic acidemia, weight

Introduction

Methylmalonic acidemia (MMA) is a rare metabolic disorder that is inherited as an autosomal recessive trait, occurring in 1:50,000 to 1:80,000 newborns.[1] MMA encompasses a heterogeneous group of disorders that are characterized by impaired metabolism of methylmalonic acid that is generated during the metabolism of certain amino acids (isoleucine, methionine, threonine, and valine), odd-chain fatty acids and cholesterol.[2] These disorders are due to a deficiency of the adenosylcobalamin-dependent enzyme methylmalonyl-CoA mutase (*MCM*, EC 5.4.99.2) or a defect in cobalamin metabolism.[2] At least 8 different complementation groups (*mut*^{0}, *mut*$^-$, *cblA*, *cblB*, *cblC*, *cblD*, *cblF*, and *cblH*) cause MMA.[3] Patients with the *mut*^{0} defect have undetectable *MCM* activity, and typically present during the newborn period.[4] Most of these patients with *mut*^{0} type of MMA may die early, before a diagnosis can be made, and those who survive often have a complicated clinical course with significant neurodevelopmental handicap.[5] Conventional therapy of MMA consists of dietary management, which can be supplemented with special formula that does not contain isoleucine, methionine, threonine or valine, L-carnitine supplementation, and inhibition of intestinal bacterial propionate production with oral antibiotics.[6] Furthermore, successful peritoneal dialysis has been reported in neonatal MMA patients with hyperammonemia,[7,8] and hemodialysis is strongly suggested nowadays.[1] However, poor feeding, poor growth, and intractable skin erosions are common findings in patients with MMA despite aggressive management with conventional therapy.[9] Growth hormone (GH) therapy

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was shown to be beneficial in growth and metabolic control in a 4.5-year-old boy[9] and in an 11.9-year-old girl,[10] both of whom had *mut*^{0} type MMA. However, GH therapy has never been reported in neonatal patients with MMA. Therefore, we present our experience with 4 neonatal MMA (*mut*^{0} type) patients who were managed with conventional and GH therapies, and clinically evaluate the beneficial effects of GH therapy in neonatal MMA patients.

Methods

Patient reports

Patient 1

This male neonate was born to healthy non-consanguineous Taiwanese parents at 40 weeks of gestation and weighed 2,920 g. Poor activity with elevated serum levels of propionylcarnitine (C3, 19.18 μM; normal, <7 μM) and elevated C3/acetylcarnitine ratio (C3/C2, 1.18; normal, <0.25) detected by newborn screening using tandem mass spectrometry (MS/MS) were noted at 5 days of age. The patient was then referred to our hospital for confirmatory testing and management.

On admission, he was mildly dehydrated and lethargic. The results of laboratory investigations performed on admission are shown in Table 1. These laboratory findings demonstrated the presence of leukopenia, anemia, ketotic hypoglycemia, hyperammonemia, metabolic acidosis, and hyperglycinemia, which were compatible with organic acidemia. Organic acid analysis of urine demonstrated increased excretion of methylmalonic acid, leading to the diagnosis of MMA. The *mut* MMA phenotype was established by measuring *MCM* activity in lymphocytes from the patient's peripheral blood. *MCM* activity was undetectable in the patient's lymphocytes (<0.05 nmol/min/mg protein *vs.* the normal control value of 3.8 nmol/min/mg protein), therefore defining a *mut*^{0} MMA phenotype. Direct sequencing of genomic DNA showed G-to-A transition at position 323 (c.323G>A) and C-to-T transition at position 1741 (c.1741C>T), respectively.

The patient received conventional therapy (dietary management, L-carnitine supplementation, and oral antibiotics) with peritoneal dialysis after admission. His serum ammonia levels fell (from 475 μg/dL to 37 μg/dL) and metabolic acidosis was corrected (pH, from 7.29 to 7.44; anion gap, from 20.2 mmol/L to 13.2 mmol/L) in 48 hours. However, the patient had persistently elevated serum levels of C3 (maximum of 31.70 μM), which failed to respond to conventional therapy. Furthermore, poor feeding, poor growth (his weight showed an increase of 142 g in the 1st month of admission) and skin erosions, which progressively developed on the face, trunk, buttocks and 4 extremities, were found during the 1st month of admission despite aggressive management with conventional therapy. After 1 month, GH therapy was prescribed. Subsequently, the patient's weight showed obvious increases in the 2nd and 3rd months of admission (Figure 1). His appetite and skin erosions also gradually improved after GH therapy.

Patient 2

This female neonate was born to healthy non-consanguineous Taiwanese parents at 38 weeks of gestation and weighed 2,900 g. The 1st MS/MS newborn screening performed at 2 days of age showed elevated serum level of C3 (12.44 μM) and elevated C3/C2 ratio (0.81). The 2nd MS/MS test performed at 5 days of age showed a lower serum level of C3 (8.99 μM) and lower C3/C2 ratio (0.67). However, the 3rd test performed at 7 days of age showed an unusually elevated serum level of C3 (14.98 μM) and elevated C3/C2 ratio (1.86). The patient was asymptomatic until 8 days of age, and recurrent vomiting subsequently presented. MMA was highly suspected, and the patient was immediately referred to our hospital for confirmatory testing and management.

The results of the laboratory investigations performed on admission are summarized in Table 1, and *mut*^{0} type MMA was the diagnosis. The patient received conventional therapy with peritoneal dialysis after admission. Her serum ammonia levels fell (from 634 μg/dL to 47 μg/dL) and metabolic acidosis was corrected (pH, from 7.29 to 7.41; anion gap, from 22.4 mmol/L to 13.4 mmol/L) in 45 hours. The difference in management from that of patient 1 was that GH therapy was immediately prescribed on admission, and her weight subsequently showed significant increases, in contrast to that of patient 1 during the 1st month of admission (Figure 1). Slight skin erosions were found over the perianal area, but were much improved after intensive skin care.

Patient 3

This female neonate was born to healthy non-consanguineous Taiwanese parents at 38 weeks of gestation and weighed 2,652 g. Shortness of breath with elevated serum level of C3 (16.65 μM) and elevated C3/C2 ratio (0.58) detected by MS/MS newborn screening were noted at 3 days of age. She was referred to our hospital for confirmatory testing and management.

Table 1. Patient characteristics and laboratory investigations of the 4 neonatal patients with methylmalonic acidemia (MMA)

	Normal values	Patient 1	Patient 2	Patient 3	Patient 4
Parents		Non-consanguineous	Non-consanguineous	Non-consanguineous	Non-consanguineous
Sex		Male	Female	Female	Male
GA (wk)		40	38	38	37
BW (g)		2,920	2,900	2,652	2,780
Age at onset (d)		5	8	3	3
Chief complaint		Poor activity	Recurrent vomiting	Shortness of breath	Shortness of breath
Initial C3 (μM)	< 7	19.18	12.44	16.65	12.39
Initial C3/C2	< 0.25	1.18	0.81	0.58	0.77
WBC (/mm^3)	9,000–35,000	7,000	7,200	3,300	7,400
Hb (g/dL)	15–20	13.8	11.4	13.7	12.9
PLT (/mm^3)	250,000–450,000	389,000	318,000	89,000	461,000
ALT (IU)	1–25	20	44	13	34
AST (IU)	35–140	31	13	113	135
BUN (mg/dL)	4–15	16	5	20	13
Cr (mg/dL)	< 0.6	0.1	0.59	0.8	0.6
BG (mg/dL)	30–90	26	38	27	29
Serum ketones	Negative	3+	3+	3+	3+
NH_3 (μg/dL)	90–150	475	634	603	650
Blood pH	7.35–7.45	7.29	7.29	7.09	7.28
AG (mmol/L)	10–14	20.2	22.4	32.2	24.0
Glycine (μM)	110–240	633.7	486	566	552.3
UOA analysis	Negative	Increased excretion of methylmalonic acid	Increased excretion of methylmalonic acid	Increased excretion of methylmalonic acid	Increased excretion of methylmalonic acid
MCM activity*		< 0.05	< 0.05	< 0.05	< 0.05
MMA type		*mut*^{0}	*mut*^{0}	*mut*^{0}	*mut*^{0}
DNA analysis		c.323G > A, c.1741C > T	c.1280G > A, homozygote	c.1280G > A, c754_755insA	c.982C > T, homozygote

**The activity of methylmalonic CoA mutase (*MCM*) of the 4 neonatal patients with MMA was less than 0.05 nmol/min/mg protein vs. the normal control value of 3.8 nmol/min/mg protein (normal value = 1.7–12.6 nmol/min/mg protein). GA = gestational age at birth; BW = birth weight; C3 = propionylcarnitine; C3/C2 = propionylcarnitine/acetylcarnitine ratio; WBC = white blood cell count; Hb = hemoglobin; PLT = platelet count; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; Cr = creatinine; BG = blood glucose; AG = anion gap (which is [NaCl] − [Cl$^-$] − [HCO_3^-]); UOA = urine organic acid.*

On admission, she was dehydrated, lethargic and showed muscular hypotonia. The results of laboratory investigations performed on admission are summarized in Table 1, and *mut*^{0} type MMA was the diagnosis. The patient received conventional therapy with peritoneal dialysis after admission. Her serum ammonia levels fell (from 603 μg/dL to 86 μg/dL) and metabolic acidosis was corrected (pH, from 7.09 to 7.35; anion gap, from 32.2 mmol/L to 14.2 mmol/L) in 41 hours. GH therapy was immediately prescribed on admission, and her weight subsequently showed significant increases, in contrast to that of patient 1 during the 1st month of admission (Figure 1). Slight skin erosions were found over the perianal area, but were much improved after intensive skin care.

Patient 4

This male neonate was born to healthy non-consanguineous Taiwanese parents at 37 weeks of gestation and weighed 2,780 g. At 3 days of age, shortness of breath, poor feeding, and lethargy were noted at the hospital where he was born. Laboratory tests performed there showed the following: white blood cell count, 9,500/mm^3; hemoglobin, 13.5 g/dL; platelet count, 330,000/mm^3; alanine transaminase, 43 IU/L; aspartate transaminase, 90 IU/L; blood urea nitrogen, 3.0 mg/dL; creatinine, 0.7 mg/dL; blood glucose, 25 mg/dL; serum ammonia, 750 μg/dL; arterial blood gas, pH 7.10; anion gap, 31 mmol/L. These laboratory findings were compatible with organic acidemia, and at that time, elevated serum level of C3 (12.39 μM)

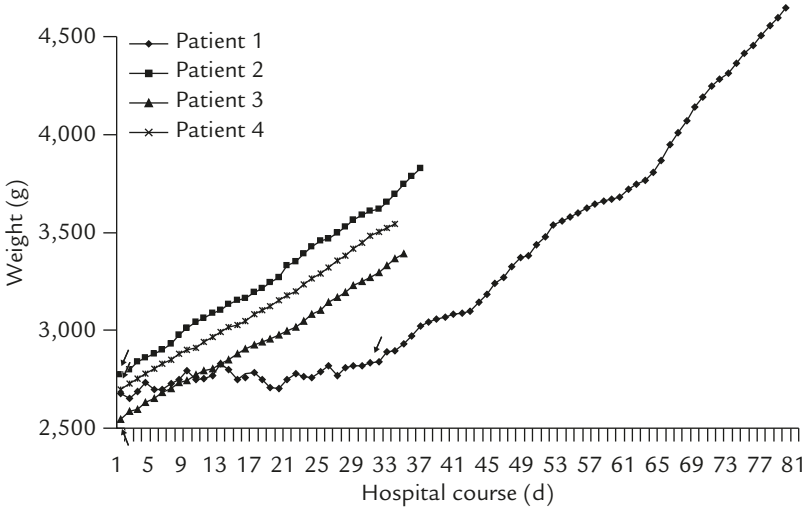

Figure 1. Effects of growth hormone (GH) therapy on the weight gain of the 4 neonatal patients with methylmalonic acidemia. GH therapy was prescribed for patient 1 after 1 month of admission, but was immediately prescribed for patients 2, 3 and 4 on the 1st day of admission. The arrows indicate the 1st day of GH therapy.

and elevated C3/C2 ratio (0.77) were detected by MS/MS newborn screening. The patient was immediately referred to our hospital for confirmatory testing and management.

The results of the laboratory investigations performed on admission are presented in Table 1, and *mut*^{0} type MMA was the diagnosis. Of note, this patient received conventional therapy with hemodialysis, which was different from patients 1, 2 and 3. His serum ammonia level fell (from 650 μg/dL to 73 μg/dL) and metabolic acidosis was corrected (pH, from 7.28 to 7.36; anion gap, from 24.0 mmol/L to 14.4 mmol/L) in 25 hours. GH therapy was also immediately prescribed on admission, and his weight subsequently showed significant increases, in contrast to that of patient 1 during the 1st month of admission (Figure 1), and no skin erosions were found.

The 4 neonatal patients with *mut*^{0} type MMA were identified through MS/MS newborn screening for elevated C3 levels. Conventional therapy included dietary management (with the special formula XMTVI Analog™, a methionine-, threonine-, valine-free and isoleucine-low powdered infant formula, from SHS, Liverpool, Merseyside, UK), L-carnitine supplementation (100 mg/kg/day), and oral antibiotics (metronidazole, 20 mg/kg/day). GH therapy, 0.6 IU/kg/week subcutaneously (Genotropin®; Pfizer, New York, NY, USA) was prescribed for patient 1 after 1 month of admission (on the 31st day of admission), and was prescribed at the same dose for patients 2, 3 and 4 on the 1st day of admission. For each patient, an informed written consent was signed by at least 1 parent. C3 level was analyzed by MS/MS at the Chinese Foundation of Health every day.

Results

For patient 1, his weight showed an increase of 834 g in the 2nd month and 970 g in the 3rd month of admission, and the skin erosions gradually improved after GH therapy. For patients 2, 3 and 4, their weights showed significant increases in the 1st month of admission (817 g, 701 g and 752 g, respectively), and they did not experience any deterioration in their condition, in contrast to what was observed in patient 1. The lengths of hospital stay for patients 1, 2, 3 and 4 were 81 days, 37 days, 35 days and 34 days, respectively, and their weights at discharge were 4,650 g, 3,827 g, 3,391 g and 3,543 g, respectively. Serum levels of C3 gradually decreased in patients 1 and 2; however, elevated serum levels of C3 with fluctuations were found in patients 3 and 4 (Figure 2).

Discussion

The management of *mut*^{0} type MMA remains difficult. With the conventional therapy of diet control, L-carnitine supplementation and oral antibiotics, mortality is high and long-term complications are common.[1] Poor growth, one of the most common complications in patients with MMA, may be caused by both chronic illness and severely restricted protein diets.[10,11] Many patients with MMA are less than 3

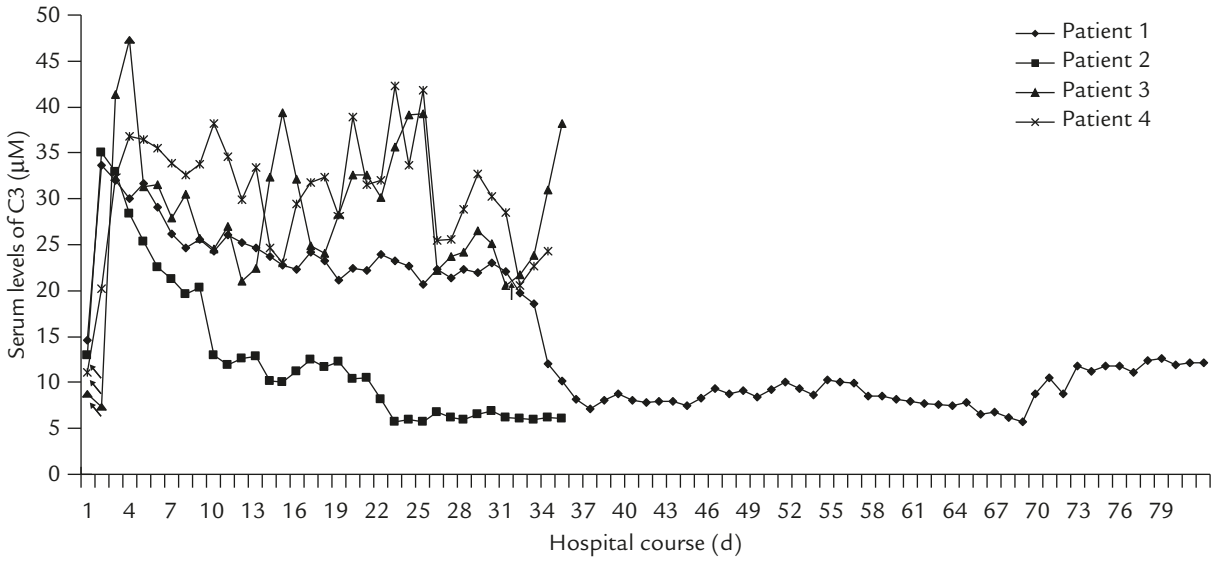

Figure 2. Effects of growth hormone (GH) therapy on the serum levels of propionylcarnitine (C3) in the 4 neonatal patients with methylmalonic acidemia. GH therapy was prescribed for patient 1 after 1 month of admission, but was immediately prescribed for patients 2, 3 and 4 on the 1st day of admission. The arrows indicate the 1st day of GH therapy.

standard deviations below the norm for both length and weight.[9] Some children had documented GH deficiency ascribed to brain damage, metabolic or nutritional perturbation.[9] Therefore, GH deficiency may be an etiologic factor in the deteriorating condition seen in patients with MMA.[9,10] Clinically, GH, due to its anabolic effect, has been shown to decrease whole-body catabolism, increase protein synthesis, accelerate wound healing, reverse growth arrest, and reduce the length of hospital stay in severely burned children.[12–14] Based on this background, GH therapy appears to be an important alternative for patients with MMA.

The clinical course of patient 1, initially managed with conventional therapy, was complicated with poor feeding, poor growth, and intractable skin erosions despite aggressive management. After 1 month of poor response, GH therapy was prescribed, and subsequently, his clinical condition was much improved. In contrast, patients 2, 3 and 4 received GH therapy immediately after admission, and subsequently, their condition did not deteriorate, which is in sharp contrast to the course of patient 1. The improvement in the clinical condition of the neonatal patients with MMA confirmed our thoughts on the effectiveness of GH therapy.

Elevated serum levels of C3 were persistently found after GH therapy in patients 3 and 4. The metabolic effects of GH therapy on reducing serum C3 levels seem to be indeterminate, although decreased serum levels of C3 were gradually found in patients 1 and 2. Notably, both patients 3 and 4 demonstrated much clinical improvement after GH therapy despite persistently elevated serum C3 levels. Theoretically, higher serum levels of C3 indicate more severe illness. However, our clinical findings seem to show that elevated serum C3 levels are unrelated to the clinical manifestations of patients with MMA. Thus, the relationship between serum C3 level and the clinical manifestations of MMA remains to be determined.

Liver transplantation is considered to increase metabolic homeostasis and protect against metabolic decompensation in patients with MMA. It can provide an improvement in quality of life due to the mitigation of protein restriction, decreasing frequency of acute decompensation, and alleviation of the state of the disease.[15]

Successful liver transplantation has been reported in infants with a median age of 7.4 months and median weight of 5.8 kg.[16] Growth improvement of patients with MMA resulted in the clinical benefit of these patients being able to undergo liver transplantation at an earlier age. Patients 1, 2 and 3 have undergone liver transplantation, and are currently doing well.

Our clinical findings suggest that GH therapy has potentially beneficial effects in neonatal patients with MMA, and we hope that our experience can provide some preliminary data so that more research can be focused on GH therapy in patients with MMA. Nevertheless, determining the optimal doses of GH therapy and the long-term prognosis for those with poor growth will require extensively controlled studies.

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