Methylmalonic Acidemia: Can Treatment be Improved?

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Abstract: Methylmalonic acidemia (MMA) is a severe metabolic disorder, particularly with complete deficiency of methylmalonyl-CoA mutase. Dietary restriction has led to overt signs of deficiencies including skin rashes, hair loss, and poor growth. More liberal intake of the restricted amino acids has resulted in better growth and less frequent episodes of illness.

Keywords: MMA, hyperammonemia, carnitine, carglumic acid, newborn screen.

INTRODUCTION

In normal metabolism, methylmalonyl-CoA mutase degrades L-Methylmalonyl-CoA to Succinyl-CoA. Decreased activity of this enzyme, as seen in methylmalonic acidemia (MMA), causes the accumulation of methylmalonic acid in the body, with various detrimental effects as seen in Figure **1**. MMA is a disorder of the metabolism of the amino acids isoleucine, methionine, threonine, and valine. Over 60% of confirmed cases of MMA are due to mutations in methylmalonyl-CoA mutase, and of these, 78% are *mut*^{0} mutations [1], with no residual enzyme activity.

The development and implementation of neonatal screening allows for the early identification of affected infants with MMA [2]. Patients with *mut*^{0} typically present within the first few days of life [3]. Typically, those with MMA *mut*^{0} have severe neurological manifestations of the disease [4].

The recommended treatment for MMA includes a low protein, high-energy diet in sufficient ratios to support normal growth and development [5]. However, emphasis is frequently placed on restriction of essential metabolites, leading to inadequate protein and energy intake, resulting in poor growth, hair loss, and skin rashes [6]. This case report demonstrates that adjusting dietary intake resulted with improved growth and fewer episodes of metabolic decompensation.

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CASE REPORT

The patient presented shortly after birth with acidosis and hyperammonemia, and then progressed to a semi-comatose state. At 3-4 days of age, a diagnosis of MMA was made and further study confirmed *mut*^{0}. The baby improved after appropriate treatment and was discharged.

Initial long-term treatment was outlined as 0.5-0.7 g/kg natural protein. Medical food allowed 1.1 g/kg of protein. Supplementation with 100 mg/kg levo-carnitine per day and 2.7-5.0 ml Bicitra per day (Sodium citrate 500mg/citric acid 334mg per 5 mL). Caloric intake was about 100 cal/kg, less than normal intake for a child this age. A G-button was placed for poor appetite and emergency feedings.

The patient was referred to our clinic at 3.5 years of age due to poor growth, hair loss, skin rashes, and frequent episodes of metabolic decompensation that required hospitalization. The metabolic episodes occurred at a frequency of 10-12 episodes per year. Height and weight were found to be less than 5th percentile (Figures **2** and **3**). The patient also had low blood concentrations of isoleucine, valine, leucine, and methionine. Arginine levels were consistently low, indicating over-restriction of amino acids. Further testing revealed low levels of pre-albumin and albumin.

The nutritional regimen was modified and the patient was placed on 1.2-1.5 g/kg/day natural protein and 2.0 – 2.5 g/kg/day of medical formula, as well as 50 mg/kg levocarnitine, 50 mg/kg acetyl-carnitine and

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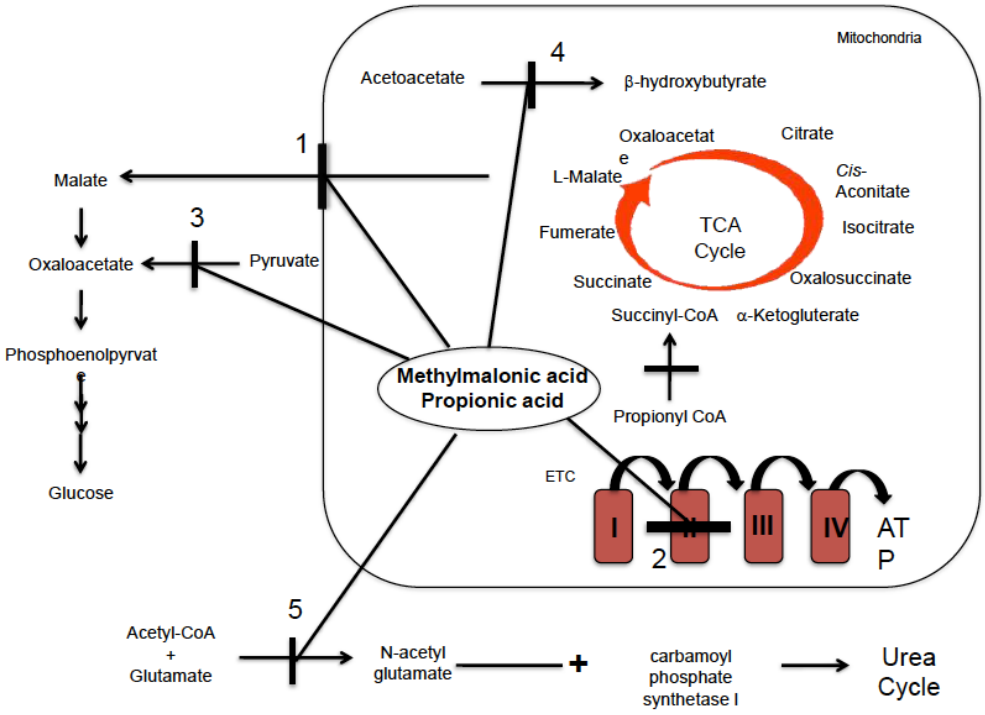

Figure 1: Biochemical pathway of methylmalonic acid in body.

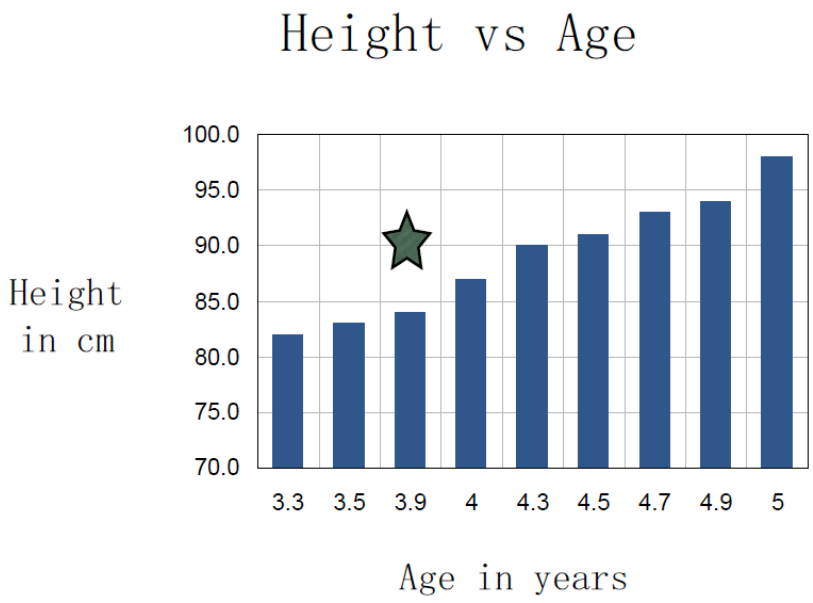

Figure 2: Depicts height versus age in this patient. Point of dietary change indicated by asterisks.

30-40 mL/day Polycitra K (Potassium citrate 1100mg/citric acid 334mg per 5 ml). Daily caloric intake was increased to 130cal/kg. No other changes were made to the patient's dietary regimen.

RESULTS

Metabolites pre and post dietary changes are shown in Figure **4**. The patient began to gain weight (Figure **3**) and parents reported an improved energy level. In addition to improved growth, the patient experienced fewer episodes of metabolic acidosis, with no episodes requiring hospitalization, and was not hospitalized for two years following the adjusted dietary treatment.

DISCUSSION

Failure to thrive in patients with methylmalonic acidemia is common. The lack of adequate growth

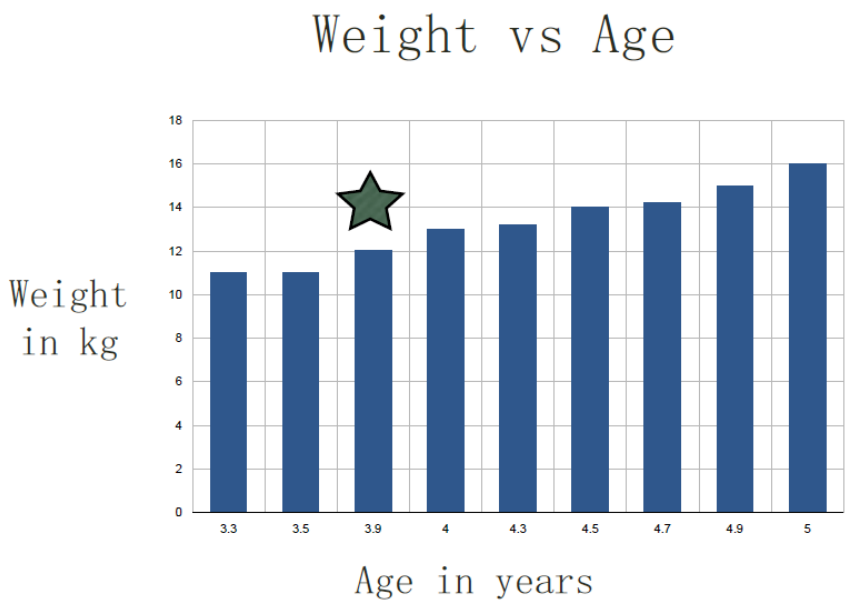

Figure 3: Depicts weight versus age in this patient. Point of dietary change indicated by asterisks.

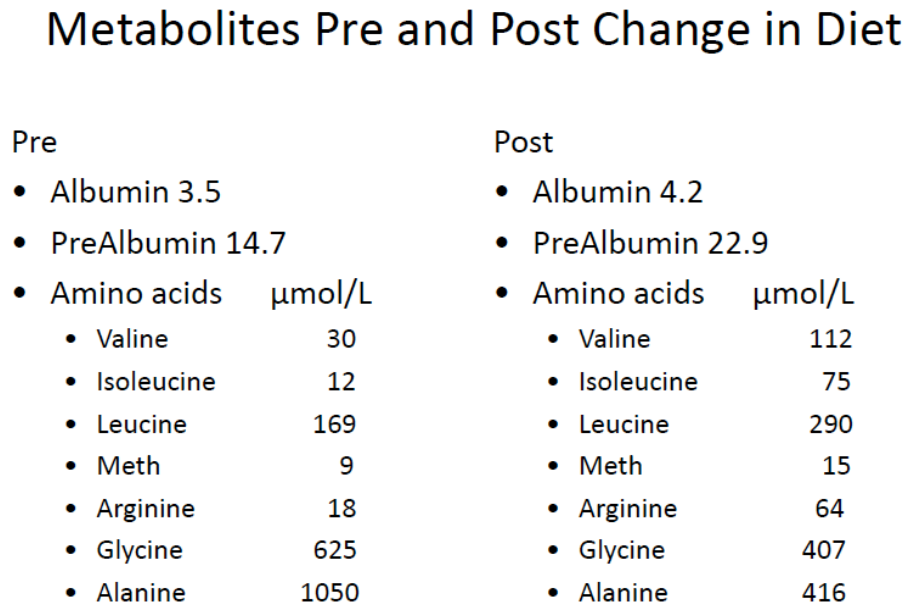

Figure 4: Metabolites pre and post dietary changes.

appears to be secondary to inadequate nutrition and over-restriction of certain amino acids. In a study by Yannicelli *et al.* [7], infants diagnosed with MMA were found to grow normally when provided adequate energy, protein and the amino acids isoleucine (ILE), methionine (MET), threonine (THR), and valine (VAL).

Low blood levels of pre-albumin and albumin, indicative of inadequate protein nutrition, has been observed in the patients followed by Kahler *et al.* [8], as well as this patient. After increasing the protein allowance to 1.2-1.5 g/kg/day natural protein and 2.0 – 2.5 g/kg/day of medical food, and increasing daily caloric intake to 130 cal/kg, albumin levels normalized, indicating the initial long-term treatment did not provide adequate protein amounts.

Hauser *et al.* [9], found that equations utilizing FAO/WHO/UNU (1985) recommendations were not a reliable guide for energy requirements of MMA patients and often failed to accurately estimate resting energy expenditures. The study by Yannicelli [6] further demonstrated that adequate linear growth was observed when protein intake was greater than 120% of the FAO/WHO/UNU recommendations and energy intakes were greater than 100% of that recommended

based on age. Protein and energy intake higher than recommended values is suggested in all patients consuming free amino acids as their primary protein source [10, 11] secondary to inefficient anabolic utilization [7, 12].

L-Carnitine supplementation of approximately 100 mg/kg/day is recommended as a prophylactic treatment [6] to bind excess metabolites that accumulate in MMA. The patient in this case responded well to 50 mg/kg levocarnitine and 50 mg/kg acetyl-carnitine. The accumulation of acyl-CoA compounds within the mitochondria in MMA depletes carnitine stores and interferes with several metabolic processes. Supplementation with L-carnitine and acetylcarnitine increases excretion of unmetabolized and potentially toxic fatty acids while supplying acetate. Patients with MMA suffer from energy generation deficiencies secondary to inadequate bioavailability of acetyl-CoA. Acetyl-L-carnitine provides both L-carnitine and a source of acetyl-CoA [13] and may be superior to L-carnitine supplementation in the treatment of MMA. In this case, a 50/50 mixture of L-carnitine/acetyl-carnitine was used although this ratio may need to be further changed in favor of acetyl-carnitine.

In addition to caloric deficiencies, MMA patients also frequently require aggressive treatment with a buffering system. Potassium citrate in the amount used seemed to prevent acidosis and also supply citrate, whose production is compromised in MMA.

Hyperammonemia is often a complication of methylmalonic acidemia due to inhibition of the synthesis of N-acetylglutamate, secondary to depressed activity of N-acetylglutamate synthase by metabolites of the organic acidemias leading to lower levels of carbamylphosphate. Carglumic acid (Carbaglu), a synthetic analog of N-acetylglutamate may need to be added to the treatment of MMA, especially in crisis. Preliminary studies have demonstrated drastic reductions in serum ammonia levels in organic acidemias [14]. Although current studies have been limited, a larger-scale trial of its efficacy in enhancing liver excretion of ammonia in patients with organic acidemias is currently under way [28].

CONCLUSION

The treatment of inborn errors of metabolism has undergone numerous changes and the recommendations for MMA need to be reassessed. In previous treatment regimens, the severe restriction of protein affected the growth of the patient. Dietary restrictions should be undertaken with caution, with generous allowance of calories to promote weight gain, and severe restriction may not be desirable. Furthermore, with negative outcomes of the disease postponed, it is possible to do such treatments as renal transplant when the patient is in better health. A collaborative study to address nutrient deficiencies is needed.

ABBREVIATION

MMA = methylmalonic academia

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Received on 31-03-2015 Accepted on 21-04-2015 Published on 30-04-2015

DOI: http://dx.doi.org/10.6000/1929-5634.2015.04.01.6