Clinical Case Report

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Management of adult-onset methylmalonic acidemia with hypotonia and acute respiratory failure

A case report

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Abstract

Rationale: Methylmalonic acidemia (MMA) is an autosomal recessive disease of organic acidemia.

Patient concerns: We report a 26-year-old male who presented with metabolic acidosis, acute renal failure required hemodialysis and acute respiratory failure required mechanical ventilation support. Progressive hypotonia of muscles made weaning from mechanical ventilator difficult.

Diagnoses: High level of serum methylmalonic acid and the *mut* genotype sequences confirmed the diagnosis of this adult-onset MMA. Two *mut* genotype sequences were found by analyzing all coding exons and exon-intron junctions. One genotype was well documented (Exon 6 Mutation, c. 1280G>A. p. G427D, heterozygous). The other *mut* genotype sequence had never been reported elsewhere (Intron 6 Novel, c. 1333-13_c. 1333-8delTTTTTC, heterozygous).

Interventions: Diet modification, medication, regular hemodialysis and physical rehabilitation. Weaning strategy adjusted with help of electrical impedance tomography.

Outcomes: The muscle power of the patient gradually recovered. Extubation of the patient was successful and he was discharged without oxygen required.

Lessons: This case gives us the lesson that MMA can be newly diagnosed in adult patient. A new *mut* genotype sequence was discovered. The use of electrical impedance tomography to select a suitable method for inspiratory muscle training was possible and useful.

Abbreviations: ATC = automatic tube compensation, CPAP = continuous positive airway pressure, EIT = electrical impedance tomography, IMT = inspiratory muscle training, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, MMA = methylmalonic acidemia, $PaCO_2$ = partial pressure of carbon dioxide in arterial blood, PaO_2 = partial pressure of oxygen in arterial blood, pH: = potential hydrogen, SBT = spontaneous breathing trial.

Keywords: acute respiratory failure, electrical impedance tomography, genotype sequence, inspiratory muscle training, methylmalonic acidemia

1. Introduction

Methylmalonic acidemia (MMA), an autosomal recessive metabolic disease, is a type of organic acidemia. The main cause of this disease is a defect in the conversion of methylmalonyl CoA to succinyl CoA; caused by mutations in mitochondrial methylmalonyl CoA mutase or impaired metabolism of vitamin B12 (adenosylcobalamin).[1] Most of the patients show acute deterioration, metabolic acidosis, and hyperammonemia shortly after birth. Confirmation of the diagnosis in adulthoods is rarely reported. MMA is classified into *mut* and *cbl* types. The *mut* type arises from the deficiency of methylmalonyl CoA mutase, and the *cbl* type results from errors in adenosylcobalamin synthesis.[2] Approximately 60% to 70% of MMA cases are attributable to mutations in the *mut* gene.

Here, we report on a 26-year-old male who was newly diagnosed MMA with hypotonia and acute respiratory failure. The clinical phenotypes and responses to therapy are described. A new *mut* genotype was discovered. The potential use of electrical impedance tomography (EIT) to select a suitable method for inspiratory muscle training (IMT) is discussed. Written informed consent was obtained prior to the report.

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ZZ and CCC contributed equally to this work.

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2. Case report

The patient was admitted to our emergency department because of intermittent cramping abdominal pain, nausea, vomiting, and progressive exertional dyspnea. Vomiting with dehydration and abnormal renal function were reported at 5 years of age. He grew up having a normal stature and graduated from college with normal mentality. No family history of hereditary disease was recorded. No abnormality was found in abdomen radiography. However, high anion gap metabolic acidosis (pH 6.763, $PaCO_2$ 18.8 mm Hg, PaO_2 177.4 mm Hg, bicarbonate 2.6 mmol/L, base excess –32.2 mmol/L, anion gap 44.5 mmol/L) and azotemia (blood urea nitrogen 85 mg/dL, creatinine 7.89 mg/dL) were found. Due to progressive tachypnea, paradoxical respiratory pattern, and impaired consciousness, the patient was promptly intubated, mechanically ventilated, and admitted to the intensive care unit.

The clinical manifestations were general muscle weakness, which progressed to respiratory muscle fatigue, and hypoxemic and hypercapnic respiratory failure. After aggressive fluid therapy, intermittent hemodialysis, and broad spectrum antibiotics, hemodynamic status was stabilized. Ventilator-associated pneumonia and lactic acidosis were managed. However, high anion gap metabolic acidosis persisted even after regular sodium bicarbonate infusion was administered between intermittent hemodialysis. Screenings for toxic drugs, ketoacidosis, atypical infectious pathogens, autoimmune diseases, occult hematologic, and oncologic diseases all returned negative results. Only chronic glomerulonephritis was confirmed by renal biopsy. Periodic Acid-Schiff stain revealed tubular atrophy, with no deposition of IgG, IgA, IgM, C3, and C1q. Cerebral imaging, cerebrospinal fluid, nerve conduction velocity, and electromyography also failed to result in conclusive diagnosis. Progressive atelectasis of bilateral lower lung dorsal regions was developed.

Finally, we consulted a pediatrician and inborn error screening tests indicated high level of serum methylmalonic acid (234 μmol/L, normally < 0.4 μmol/L). After excluding known single-nucleotide

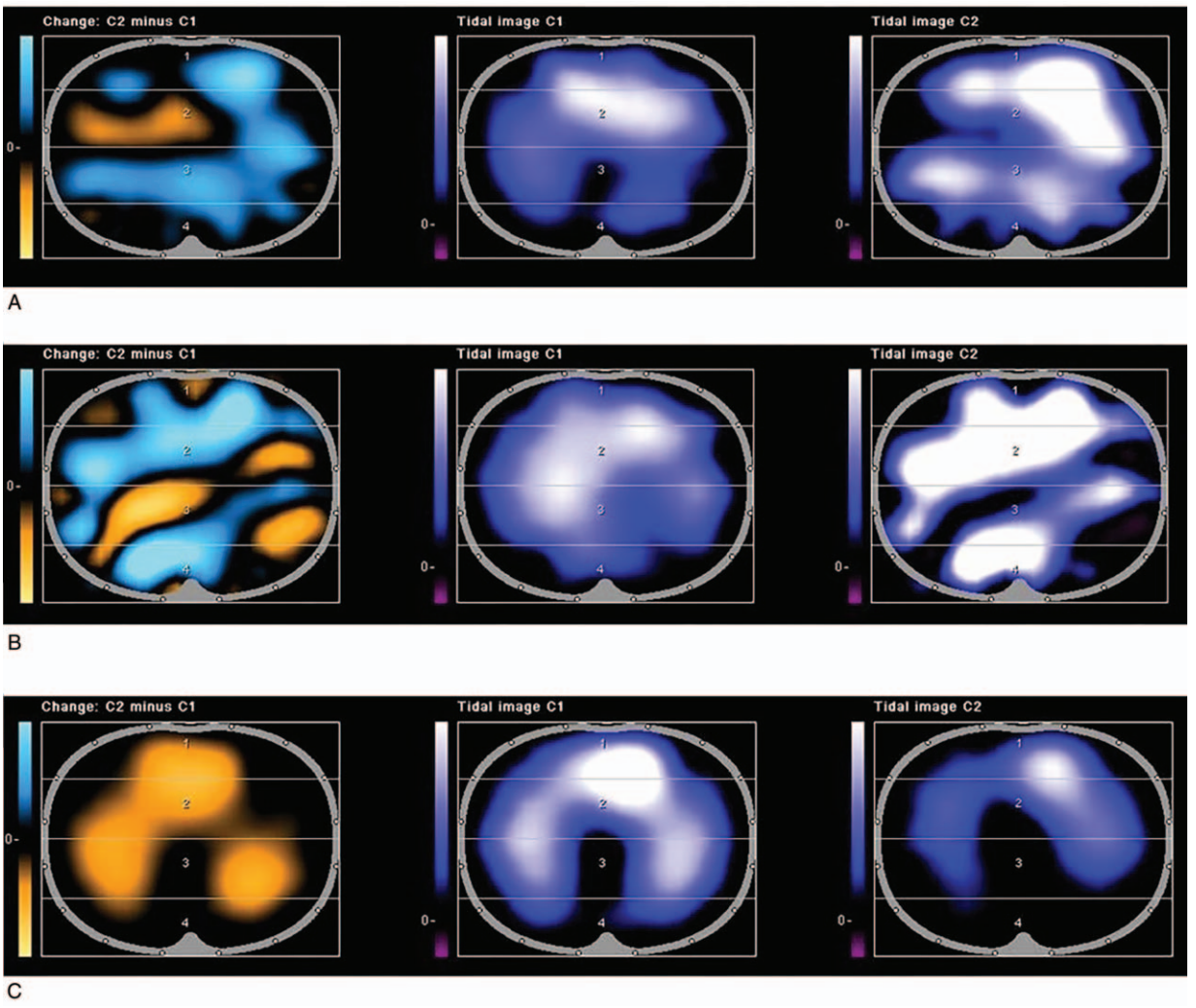

Figure 1. EIT images captured during different spontaneous breathing trials. (A) Tidal ventilation distribution at the end of external CPAP 5.0 cmH_2O (right) and at the end of assist-control ventilation (middle). Highly ventilated regions are indicated in light blue. Differences in ventilation distribution (left = right − middle) indicate the volume gain (blue) and volume loss (orange). (B) Tidal ventilation distribution at the end of the T-piece trial (right) and at the end of assist-control ventilation (middle). Highly ventilated regions are indicated in light blue. Differences in ventilation distribution (left = right − middle) indicate the volume gain (blue) and volume loss (orange). (C) Tidal ventilation distribution at the end of CPAP+100% ATC (right) and at the end of assist-control ventilation (middle). Highly ventilated regions are indicated in light blue. Differences in ventilation distribution (left = right − middle) indicate the volume gain (blue) and volume loss (orange). ATC = automatic tube compensation, CPAP = continuous positive airway pressure, EIT = electrical impedance tomography.

polymorphism, 2 *mut* genotype sequences were found by analyzing all coding exons and exon-intron junctions. One genotype, exon 6 mutation, c.1280G>A. p.G427D, heterozygous, is well documented. The other *mut* genotype sequence, intron 6 novel, c.1333-13_c.1333-8delTTTTTC, heterozygous, has never been reported elsewhere. Vitamin B12 loading test confirmed that the patient was vitamin B12 unresponsive. L-Carnitine and special diet formula (XMTVI Maxamaid; Nutrica, Dublin, Ireland) were prescribed (special protein intake 0.7 g/kg and formal formula 0.5 g/kg). One week after the special formula diet, no improvement of azotemia and metabolic acidosis with high MMA levels (1,067 μmol/L before and 442 μmol/L after hemodialysis) was measured. Deterioration of neurologic signs was observed along with quadriplegia. With the adjustment of protein intake (special protein 0.9 g/kg, formal formula 0.3 g/kg), the serum MMA level declined within 10 days (27.43 μmol/L before and 8.29 μmol/L after hemodialysis). Hypotonia improved gradually and muscle strength of the 4 limbs increased from grade one to grade 4 (Oxford scale).[3]

Progressive hypotonia made weaning from mechanical ventilation difficult (at the 15th mechanical ventilation day, maximal inspiratory pressure, MIP—10 cmH_2O, maximal expiratory pressure, MEP—14 cmH_2O). After the decrease of the serum MMA level, IMT was performed. The spontaneous breathing trial (SBT) method was selected based on EIT measurements (PulmoVista 500; Dräger Medical, Lübeck, Germany). The EIT setup was described previously.[4] Three one-hour sessions with different SBTs were performed, where ventilation distribution was monitored by EIT. Between each session, the patient was ventilated with assist-control mode for 12 hours (tidal volume 10 mL/kg ideal body weight, respiratory rate 12/min, PEEP 5 cmH_2O, I:E 1:2, inspiratory trigger flow 2 L/min, peak airway pressure < 60 cmH_2O). In session one, external continuous positive airway pressure (CPAP; WhisperFlow CPAP System 8500; Philips Respironics, Murrysville) connected with 5.0 cmH_2O ACCU-PEEP Threshold Resistors (Vital Signs Inc., Totowa) was used. Ventilation in dorsal regions increased (Fig. 1A). In session two, a T-piece was applied. Paradoxical ventilation redistribution was observed (Fig. 1B). In session three, automatic tube compensation (ATC) 100% plus external-CPAP 5 cmH_2O was used. Tidal ventilation decreased in both ventral and dorsal regions (Fig. 1C). External-CPAP was selected as the appropriate SBT for further IMT. Improvement of inspiratory and expiratory muscle strength was measured on the 61st day of mechanical ventilation (MIP –26 cmH_2O, MEP 40 cmH_2O). Extubation of the patient was successful and he was discharged without oxygen requirement. With diet modification, medication, regular hemodialysis, and physical rehabilitation, the patient gradually recovered and was discharged without disabilities.

3. Discussion

The difficulty of the case was the diagnosis of MMA. The patient was not a vegetarian but he had rarely consumed meats since childhood. According to the family's statements, the patient always felt general malaise and gastric upset after he consumed meats. A potential trigger of the onset could be a steak he ate in a social gathering 2 days before the emergency department visit. It is unknown whether the diet habit postponed the fulminant onset of clinical manifestations. MMA was diagnosed on the basis of high MMA levels and genotype analyses. The well-documented genotype, exon 6 mutation, c.1280G>A. p.G427D, heterozygous, reportedly is the leading cause of deficiency of methylmalonyl CoA mutase and refractory metabolic acidemia.[5] In addition, we found new *mut* genotype sequence, intron 6 novel, c.1333–13_c.1333–8delTTTTTC, heterozygous, which has never been reported previously. The significance of this genotype is unknown and we suspect that this *mut* genotype might be a factor that postpones the clinical manifestations until adulthood, which needs to be confirmed in a larger population.

The management of the underlying diseases in the intensive care unit was also critical. The intake of branched-chain amino acid supplements and odd-chain fatty acids was strictly restricted, since they are metabolized via the methylmalonyl-CoA pathway.[6] A low-protein diet (0.5 to 1.5 g/kg per day) containing the minimum natural protein for growth was required. Hydroxycobalamin was administered until the type of MMA was identified. L-Carnitine was administered to increase the urinary excretion of MMA.[1] Before the confirmation and management of MMA, the patient suffered from persistent hypotonia, which progressed to respiratory muscle fatigue, and it was hard to wean the patient from mechanical ventilation. Prolonged mechanical ventilation promotes diaphragmatic atrophy and contractile dysfunction.[7] EIT was proposed to guide respiratory therapies.[8] Preliminary studies indicated the potential of EIT for monitoring the weaning process.[9,10] This is the first attempt to select an SBT method via EIT. Compared to controlled ventilation, external CPAP adequately increased diaphragm activities and led to air redistribution towards dorsal regions in the patient (Fig. 1A). Ventilation distribution with a T-piece seemed unstable, which implied respiratory muscle fatigue (Fig. 1B). With CPAP+100%ATC, the support level could be too high for IMT. The positive outcome of the patient encourages further studies on the usability of EIT for SBT selection, with more subjects.

Author contributions

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