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A modified Atkin's diet for an infant with pyruvate dehydrogenase complex deficiency confirmed by *PDHA1* gene mutation

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Abstract

Pyruvate dehydrogenase complex deficiency (PDCD) is one of the most common neurodegenerative disorders associated with abnormal mitochondrial metabolism. Pyruvate dehydrogenase complex plays an important role in glucose metabolism and generation of energy from carbohydrates. Potential therapies for PDCD, include thiamine and ketogenic diet (KD), have been used with varying degrees of success. However, the KD is too restrictive, and its serious complications, particularly in early age of neonate or infancy are important drawbacks. Recently, the modified Atkins diet (MAD) for intractable epilepsy has provided balanced nutrients. The complications can be expected to be less frequent and well controlled. In this report, we describe an infant with PDCD confirmed by *PDHA1* gene mutation through high-throughput sequencing technique of whole exome sequencing, who failed to continue the KD, but made good progress on MAD.

INTRODUCTION

Pyruvate dehydrogenase complex deficiency (PDCD) is one of the most common neurodegenerative disorders associated with abnormal mitochondrial metabolism. Pyruvate dehydrogenase complex plays an important role in glucose metabolism and generation of energy from carbohydrates.[1,2] It has a large mitochondrial multienzyme complex consisting of three catalytic enzymes: pyruvate dehydrogenase (E1), dihydrolipoamide acetyltransferase (E2), and dihydrolipoamide dehydrogenase (E3).[3] There is wide spectrum of clinical symptoms from fatal neonatal lactic acidosis to mild ataxia or neuropathy. Potential therapies for PDCD, including administration of thiamine, ketogenic diet (KD), have been used with varying degrees of success. However, the KD is still too restrictive and its serious complications, particularly in early age of neonate or infancy and who requires a diet therapy for his entire lifetime are important drawbacks. The modified Atkins diet (MAD) consisted of a nearly balanced diet (60% fat, 30% protein, and 10% carbohydrates by weight). It is more tolerable and complications can be expected to be less frequent and well controlled.[1,4,5,6]

In this report, we described an infant with early onset PDCD confirmed by *PDHA1* gene mutation through targeted next generation sequencing (NGS), who failed to continue the KD, but made progress on a MAD.

CASE REPORT

A five-month-old, male patient was born at intrauterine pregnancy (IUP) 40 weeks with birth weight of 2.27 kg via vaginal delivery without any perinatal complications. At the age of four months, he developed seizure, generalized muscle hypotonia, and hyperventilation after respiratory infection. Neurologic examination showed hypotonia and a mild developmental delay. He developed metabolic acidosis and his plasma lactate level was elevated to 11.4 mmol/l and pH level was 7.2. Cerebrospinal fluid lactate was also elevated, at 7.6 mmol/l. Magnetic resonance spectroscopy of the brain showed a lactate peak in basal ganglia. Based on clinical features and laboratory findings, the patient was suspected as having underlying PDCD. We used targeted next-generation sequencing to screen pyruvate dehydrogenase complex gene mutations including

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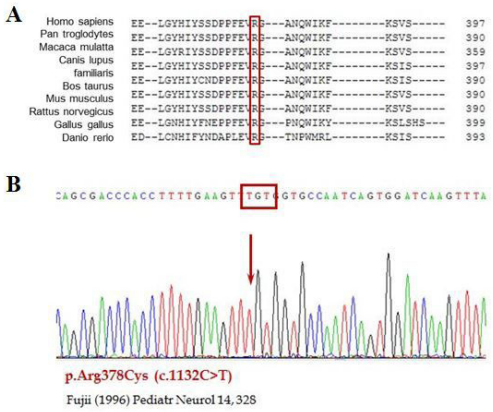

Figure 1. DNA sequencing of the patient. (A). The alignment of *PDHA1* gene across of 10 species that altered amino acids were evolutionary conserved, which suggest that the missense mutation found in this case is critical. (B). Direct sequencing in blood revealed point mutation of the *PDHA1* gene.

PDHA1 gene. A point mutation in the *PDHA1* gene *(p.Arg378Cys /c.1132C>T)* was revealed by targeted NGS. We confirmed this mutation by Sanger sequencing of *PDHA1* gene (Figure 1). We also requested specimens from both parents. Same mutation was not identified from both parents.

KD with the ratio of fat to non-fat, 3 to 1 was tried with thiamine supplement. His lactic acidosis showed improvement and he was discharged. However, after one week, he was re-admitted because of poor oral intake, lethargy, and sweating. His blood lactate level remained in the range of 2.9-4.1 mmon/l, with normal blood glucose levels (Figure 2). However, the patient had abdominal distension, irritability, and poor oral intake. We changed the diet therapy to a

Figure 2. Serum lactate levels with diet therapy. Serum lactate level remained in the range of 2.9-4.1 mmon/l during the ketogenic diet and a modified Atkins diet.

MAD with the constituents of 60% fat, 30% protein, and 10% carbohydrates by weight. This was achieved by mixing general milk formula and manufactured protein to a liquid ketogenic milk with a ratio of classic KD. For seven months, he made developmental progress with plasma lactate range under 3 mmol/l. He has not required hospitalization since changing his diet from classic KD to MAD. The compliance with MAD was also very good. He is now 13 months old and his head circumference is 44.5 cm, which is 5-10th percentile for his age. He has shown catch-up developmental progress without any neurological disabilities.

DISCUSSION

The most important role of pyruvate dehydrogenase complex is providing energy from glucose. In PDCD, a key mechanism that induces brain damage is lack of sufficient energy for brain and subsequent toxicity of lactic acidosis.[1,7] The KD provides ketones as alternative the brain. The KD is now a proven treatment of refractory epilepsy and some metabolic disorders. The classic KD is based on a ratio of fat to carbohydrate and protein of 3:1 or 4:1. The amount of protein is adjusted so that approximately 90% of calories are derived from fat with total calories restricted to 75% of the daily allowance.[3,8] Drawbacks to the use of the KD should be considered. Most children loathe the conventional KD because of its poor palatability and the gastrointestinal troubles it causes, so much so that it often results in the patients to finally give up on the diet therapy. Any modification to the conventional KD that would augment its tolerability and convenience without sacrificing its efficacy is worth trying. First, we prepared a liquid ketogenic milk developed by the authors and our colleagues. One packet of 180 mL contains 216 Kcal and has a lipid to non-lipid ratio of 4:1 in gram scale. We adjusted it to a modified Atkins diet with the constituents of 60% fat, 30% protein, and 10% carbohydrates by weight by mixing general milk formula and protein. Carbohydrates were restricted to a maximum of 10% carbohydrates per day by weight. The MAD also restricts carbohydrates, but does not restrict calories or proteins and The MAD was originally designed with the aim of proposing a less restrictive dietary treatment. It has been suggested that the risk of complications and growth retardation might be lower on MAD than on KD. Considering the balance between fat and protein, long term side effects would be reduced in comparison to the KD.

But, before resume diet therapy we need to confirm the diagnosis of this patient. So, with NGS in screening, we used high-throughput sequencing technique to screen genes associated with energy metabolisms including PDCD genes. We could easily detect *PDHA1* gene mutation from various kinds of gene mutations. Later it was confirmed by Sanger sequencing method. PDCD is of X-linked recessive inheritance. But no mutation was identified in both of the parents. In this case, NGS was very useful to confirm the diagnosis and genetic counseling.

In summary, the MAD may be a reasonable choice in long term maintenance treatment of PDCD. This is particularly so when the diet therapy have to be given from early age of neonate or infancy.

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