Clinical manifestations in two patients with pyruvate dehydrogenase deficiency and long-term survival

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Pyruvate dehydrogenase (PDH) catalyzes the irreversible decarboxylation of pyruvate into acetyl-CoA, linking glycolysis to the tricarboxylic acid cycle. PDH is composed of multiple copies of three subunits, that is, PDH (E1, EC 1.2.4.1), dihydrolipoamide transacetylase (E2, EC 2.3.1.12) and dihydrolipoamide dehydrogenase (E3, EC 1.8.1.4), along with an E3-binding protein. The E1 component is a heterotetramer of two α-subunits and two β-subunits. The gene encoding the E1a subunit (PDHA1, MIM #300502) is located on the X chromosome (Xp22.1→22.2), and all subunits are nuclear-encoded. PDH E1α deficiency (PDHAD, MIM #312170) results in lactic acidosis and hyperpyruvatemria. The spectrum of the clinical manifestations of PDHAD ranges from severe neonatal lactic acidosis with early death to intermittent ataxia with a late-onset progressive neurodegenerative course.1,2

We followed two PDHAD patients with intellectual disability and a relatively stable clinical course under careful nursing care. We previously reported the onset and diagnosis of patient 1,3,4 whereas patient 2 presents a novel mutation (c.433_435delTGT, p.C145del mutation; http://www.hgmd.cf.ac.uk). We report the relationship between their genetic backgrounds and long-term outcomes.

Patient 1 is a 38-year-old man, who had been born at full term with a birth weight of 2,670 g. He could support his head at 6 months and could stand with support at 14 months. He had a birth weight of 2,670 g. He could support his head at 6 months and could stand with support at 14 months. He was suspected because of elevated blood lactate (64.7 mg/dl) and pyruvate (5.0 mg/dl) and lactate in the CSF (58.4 mg/dl). Brain MRI and ultrasonography indicated ventricular enlargement on both sides and periventricular leukomalacia (Figure 1a,b). His brain MRI at 31 days of age showed symmetrical low-intensity signals of the basal ganglia and corpus callosum hypoplasia (Figure 1c). PDHAD was suspected because of elevated blood lactate (64.7 mg/dl) and pyruvate (5.0 mg/dl) and lactate in the CSF (58.4 mg/dl) (Supplementary Table S1). She was diagnosed with a c.433_435delTGT heterozygous mutation in PDHA1 exon 5 (NM_000284.3) (Figure 1d–f), confirmed to be de novo. She was treated with vitamin B₁, biotin, lipoate and dichloroacetic acid (DCA). Although hyperlactacidemia and hyperpyruvic acidemia improved to 18.4 mg/dl and 1.78 mg/dl, respectively, lactate levels in the CSF (44.1 mg/dl) had not decreased 12 days after administration. As the ventricular enlargement and brain atrophy progressed with time, DCA was discontinued at 3 years of age. She was hospitalized three times because of decreased appetite, convulsions and aspiration pneumonia. She underwent cardio-plasty at 4 years of age because her gastroesophageal reflux became severe. She then demonstrated good nutritional status and did not develop aspiration pneumonia again. She is now 10 years old and has a developmental quotient of < 20 on the Enjoji scale of infant analytical development and an unmeasurable intelligence quotient. She is in a stable physical state and goes to a special school.

This case report was approved by the Ethics Committee of the Faculty of Life Science, Kumamoto University. Written informed consent was obtained from the families of both patients reported herein.

No report has been published regarding patients with PDHAD who have survived as long as patient 1. Although patient 2 has fetal-onset type PDHAD, she presents with a relatively stable condition and is in a stable physical state.
health condition. Patel et al.\(^5\) reported that 243 of 371 patients with PDHAD (65.5%) were alive at 6 months of age, but only 10 patients (2.7%) were still alive at 20 years of age. Death was associated with high blood lactate levels and low PDH activity. The common PDHA1 mutations are at amino acid position 263, 302 or 378. Some patients with c.R263G survive for 7–18 years.\(^6\)–\(^8\) Patient 1 presented with p.R263Q and has survived for 38 years to date. The enzyme activity is variable between male patients with p.R263G and p.R263Q (16–77%; Table 1). According to Barnerias et al.\(^9\) and DeBrosse et al.,\(^10\) within specimens from the same individual with PDHA1 mutations and even within the same specimen, there are large variations in PDH activity. This was evident when PDH activity was compared between cultured skin fibroblasts and fresh blood lymphocytes from the same individual. DeBrosse et al.\(^10\) reported a significant difference in the survival of males with PDHA1 mutations whose fibroblast PDH activity was \(\geq 35\%\) of the reference mean compared with those whose PDH activity was \(< 35\%\) of the mean. However, there was no significant correlation between PDH activity in fibroblasts from male or female patients with PDHA1 mutations and their intellectual outcome. Therefore, male subjects with PDHA1 mutations whose fibroblast PDH activity is \(\geq 35\%\) are more likely to have long-term survival, similar to patient 1 reported here.

The c.433_435delTGT (p.C145del) identified in patient 2 has never been reported. Gene mutations around amino acid 145 in exon 5 are summarized in Table 1. Patients with p.R141Q or p.G144del present residual activity, and the activity of p.C145del might be relatively high, although this information is not available. However, investigating PDH activity remains difficult, particularly in female patients with PDHA1 mutations, because of tissue-

Figure 1. Brain imaging and PDHA1 DNA sequence in patient 2. Brain ultrasonography (a) coronal section and (b) sagittal section images) demonstrated enlarged lateral ventricles on both sides and cystic lesions. (c) Brain MRI showed enlarged lateral ventricles on both sides and cystic changes around the lateral ventricles. (d) Direct PDHA1 DNA sequencing of white blood cell DNA in patient 2. Subcloning of PCR products generated from white blood cell DNA from patient 2 demonstrated a mixture of the normal sequence (e) and the c.433_435delTGT (p.C145del) mutation (f).
dependent X-inactivation. The defect might need to be sought and confirmed in several tissues by techniques such as enzymatic activity assay and immunohistochemistry. Tissue-specific skewed X-chromosome inactivation gives rise to the variability of female PDHAD.

The effective treatment for PDHAD is a ketogenic diet with carbohydrate restriction. Patients 1 and 2 consumed a ketogenic diet. Biotin was administered to both patients to activate their PDH complex (PDHc) activity was measured in patient 2, lactate levels decreased in the blood, but not in the CSF and stabilizing the PDH complex. After DCA administration in patient 2, lactate levels decreased in the blood, but not in the CSF and neurological symptoms might be observed after at least a month of DCA administration.

Although patient 1 achieved head control late, he underwent a detailed examination for PDHAD as late as at 19 months. Intervention at an earlier stage might have improved the outcome. He was repeatedly hospitalized during his childhood of female PDHAD. In conclusion, early and long-term interventions should be tailored according to each patient’s symptoms and problems. Good nutritional conditions should be maintained, while controlling convulsions and preventing aspiration pneumonia.

**HGV DATABASE**

The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.1358.

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**COMPETING INTERESTS**

The authors declare no conflict of interest.

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