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MRI Features of 4 Female Patients with Pyruvate Dehydrogenase E1 alpha Deficiency

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Abstract

Pyruvate dehydrogenase complex is a key intramitochondrial multienzyme complex required for the conversion of pyruvate to acetyl-CoA. The majority of patients with pyruvate dehydrogenase deficiency have a defect in the E1 alpha subunit, associated with mutations in the *PDHA1* gene. In this report, we submit detailed magnetic resonance images in four affected female patients with *PDHA1* mutations, who present with severe cortical atrophy, dilated ventricles, and an incomplete corpus callosum. In one of these patients, the MRI pattern prompted molecular diagnostic testing when enzymatic testing was normal. We underscore that this constellation of features, which may be misdiagnosed as periventricular leukomalacia, illustrate a pattern highly suggestive of a deficiency of pyruvate dehydrogenase E1 alpha in female patients and should trigger appropriate diagnostic investigations.

Keywords

Lactic Acidosis; Malformations of Cortical Development; Mutation

Introduction

Pyruvate dehydrogenase (PDH) deficiency is a common cause of primary congenital lactic acidosis [1–5]. The PDH enzyme complex is a key intra-mitochondrial complex [6] which catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, thereby controlling the flow of substrates from the glycolytic pathway to the citric acid cycle. Defects in the E1α subunit gene (*PDHA1*; EC 1.2.4.1) on Xp21.3 account for the majority of cases of PDH deficiency [3, 7].

The classical biochemical features of PDH deficiency consist of an elevated blood lactate and pyruvate level and a normal lactate-to-pyruvate ratio [3]. However, the neurological presentation of PDHA1 deficiency is variable, and often differs between males and females

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[1–5]. Imaging features in males with PDHA1 deficiency are well recognized, and include subependymal cysts [8]; agenesis of the corpus callosum [2]; or a Leigh-like picture frequently accompanied by leukoencephalopathy [2, 8–10]. Females with PDHA1 deficiency often have a more severe clinical phenotype [1–4]. Previous radiological or neuropathological [11, 12] reports describe severe structural brain anomalies in affected females, including absence or hypoplasia of the corpus callosum, very thin cerebral mantle, and ventriculomegaly. While MRI findings in PDHA1 deficient females have been described [3, 5, 11, 13–15], we underscore the importance of MRI pattern recognition as a diagnostic tool in this disorder.

We analyzed MR imaging features in four female patients with PDHA1 deficiency. In all 4 patients the phenotype was highly suggestive of the diagnosis.

Patient 1

Patient 1 was born after a full-term gestation. Birth weight was 2.9 kg and occipitofrontal circumference was 33.5cm (10^{th} percentile). Due to developmental delay, the patient was evaluated by a pediatric neurologist at 4 months of age. Neurological exam revealed an occipitofrontal circumference of 36.5 cm (3–4 SD below the mean) and an appropriate suck and cry, but she did not smile or reach for toys. Visual tracking was absent. She also displayed significant axial and appendicular hypotonia. Initial serum lactate (7.3 mM; NR 1 – 1.7 mM), and pyruvate (0.65 mM; NR 0.03 – 0.17 mM), were both elevated, but the lactate/pyruvate ratio was normal. Brain MRI was performed at 4 months (Figure 1, Patient 1, A–C). Pyruvate dehydrogenase complex activity, assayed in fibroblasts, was decreased (29% of the mean). *PDHA1* sequencing demonstrated a *de-novo* heterozygous invariant splice site mutation, c.899 + 1 g>c.

Patient 2

Patient 2 was born at 35 weeks gestation. Asymmetric lateral ventricles, with progressive enlargement, had been observed on prenatal ultrasound. Birth weight was 2.5 kg, and occipitofrontal circumference at birth was not reported. In the neonatal period, she had marked hypotonia and feeding difficulties. At 5 months of age, she presented with infantile spasms and subsequently developed intractable epilepsy. Serum lactate (3.4 mM; NR 1–1.7 mM) and pyruvate (0.25 mM NR; 0.03–0.17 mM), were elevated at 5 months and the lactate/pyruvate ratio was normal. Brain MRI was performed at 5 months (Figure 1, Patient 2, A–C). Activity of the pyruvate dehydrogenase complex in fibroblasts was decreased (41% of the mean). Follow-up sequencing of *PDHA1* demonstrated a *de-novo* heterozygous mutation, c.449 G>A.

Patient 3

Patient 3 was born at 36 weeks gestation. Birth weight was 2.2 kg, and occipitofrontal circumference was 30.5 cm (4–5 SD below the mean). In the neonatal period, she was noted to have hypotonia, contractures and feeding difficulties, but had a good suck and cry, and normal reflexes. Initial serum lactate (5.0 mM; NR 1 – 1.7 mM) was elevated. Repeat measurement revealed a lactate of 2.9 mM and pyruvate of 0.24 mM (NR 0.03 – 0.17 mM), with a normal lactate/pyruvate ratio of 12. Brain MRI was performed on day of life 1 (Figure 1, Patient 3, AB). Activity of the pyruvate dehydrogenase complex in fibroblasts was decreased (42% of the mean) and *PDHA1* sequencing demonstrated a *de novo* heterozygous mutation, c.1011_c.1031duplication21.

Patient 4

Patient 4 was born at 37 weeks gestation after pre-term labor at 32 weeks. The neonatal period was significant for transient neonatal jaundice, as well as milk intolerance and reflux. Infancy was notable for global developmental delay, microcephaly, poor visual skills, irritability, obstructive sleep apnea and chronic congestion. Initial investigations revealed an elevated serum lactate (7.6 mM; NR 1.0–3.3 mmol/L) and elevated plasma alanine (1363 μM; NR 96–798). Repeated measurements showed elevated pyruvic acid (0.37 mM; NR 0.03–0.17), elevated lactate (4.7 mM; NR 1.0–1.7) and a normal lactate/pyruvate ratio of 13. Initial brain MRI was performed at 3 months of age and a repeat brain MRI/MRS was performed at 11 months (Figure 1). Activity of the pyruvate dehydrogenase complex was surprisingly normal in blood lymphocytes. However, because of typical MRI findings combined with a high clinical suspicion, *PDHA1* sequencing was pursued prior to skin biopsy for fibroblast enzymatic testing. This detected a heterozygous novel missense variant, c. 680A>G (p.Y227C).

Brain Imaging

Brain MRI in all four patients (Figure 1) revealed asymmetric enlargement of the lateral and third ventricles, sparing the 4th ventricle. Patients 1, 2, and 4 presented with intraventricular septations. In all patients there was prominent paucity of cerebral white matter volume and a small pons. All patients exhibited an incomplete corpus callosum: specifically, parts of the genu and anterior body were present but the posterior body and splenium were absent, as confirmed by review of axial T2 and sagittal T1 images. Hyporotated hippocampi and small optic nerves with a low normal-sized optic chiasm were observed in patients 1, 2, and 4 but selected imaging of the optic nerves and hippocampi were not available for patient 3. Patient 3 also had subcortical cysts and asymmetrical subependymal cysts in the caudothalamic grooves. MR spectroscopy of the basal ganglia in patient 1 revealed a lactate peak (not shown). Head CT scans performed in patients 1 and 3 did not show calcifications.

Discussion

Female patients with PDHA1 deficiency often have more severe brain anomalies [1–4] than their male counterparts. This difference between the sexes is hypothesized to be as a result of differences in X-chromosome number. In affected males, who possess a single X-chromosome, a uniform population of cells with a deleterious *PDHA1* allele that essentially abolishes enzyme activity is thought to be embryonically lethal [1, 2]. Only affected male fetuses with significant residual enzyme activity survive to the neonatal period [1, 2]. Consequently, newborn males with PDHA1 deficiency typically do not present severe structural brain anomalies at birth. In contrast, in females, random X-inactivation leads to expression of either the mutant or normal allele in neuronal cells [1, 2]. Therefore, even the most deleterious of *PDHA1* alleles can result in a viable female pregnancy given a favorable lyonization: cells expressing the normal allele ensure fetal survival, whereas affected cells are non-viable, and their death results in malformations of the brain [1–4], such as those observed in our patients. Non-uniform patterns of lyonization may also result in diagnostic challenges, as is presumably the case in patient 4, in whom enzymatic evidence of PDH deficiency could not be established in lymphocytes.

Severe decrease in white matter volume, dilated ventricles with ventricular septations or parenchymal cysts and partial-to-complete agenesis of the corpus callosum have been previously reported in association with PDHA1 deficiency in female patients [3, 5, 11, 12, 14–16]. Based on MR imaging alone, it could be difficult to differentiate this pattern from other processes, such as cystic periventricular leukomalacia or postinfectious versus term

hypoxic-ischemic injuries. However, the findings of markedly asymmetric white matter involvement are less likely to be seen in periventricular leukomalacia or hypoxic ischemic injury unless associated with a unilateral vascular event. Ventricular enlargement in PDH1 deficiency is probably the result of severe white matter volume loss. All four patients had a pattern of lateral and 3rd ventricle enlargement with normal size of the 4th ventricle. It is possible that in addition to decreased white matter volume, a structural abnormality of the aqueduct contributed to ventricular dilatation[17]. The observed small size of the pons may be due to hypogenesis/hypoplasia or secondary to developmental loss of cerebral white matter and decreased volume of descending long tracts. Similarly, the abnormalities of the corpus callosum may be due to hypogenesis/hypoplasia or related to prenatal white matter destruction. The difference between structural defects due to a prenatal destructive process secondary to a metabolic defect of selected cells[4] versus true hypogenesis/hyplasia is difficult to determine in this disorder. Ventricular septations and intraparenchymal cysts may also be the result of a destructive processes and may represent areas of incomplete porencephaly or cystic periventricular encephalomalacia.

Several other non-specific features were observed, including hyporotated hippocampi and small optic nerves. Hippocampal malrotation or “inversion” is seen in association with a variety of cortical malformations[18] or in the setting of hydrocephalus[19]. The significance of small size of the optic nerves in this setting is unclear. MR spectroscopy of the basal ganglia in patient 1 revealed a lactate peak, as has been previously described in PDH complex deficiency [15].

With regard to the genetics *PDHA1*, we add four novel mutations to the 116 currently described in the Human Gene Mutation Database *PDHA1* mutation database (www.hgmd.cf.ac.uk). One of these mutations c899 + 1 g>c, affects the first nucleotide of intron 9 disrupting the canonical AGgt donor splice site. Only one of the other seven known *PDHA1* splicing mutations is also intronic, and occurs in the acceptor splice site of intron 9 [20], leading to activation of a cryptic upstream splice site. The remaining known splicing mutations affect exonic splicing enhancer motifs in exons 5 [21], 6 [22], and 7 [23].

In summary, we emphasize the constellation of MRI findings in female patients with PDHA1 deficiency, including an abnormal corpus callosum, asymmetric ventricular dilatation, ventricular septations and/or parenchymal cysts, and a small pons. The recognition of this MRI pattern, especially in the context of an elevated blood lactate and a normal lactate-to-pyruvate ratio, should prompt further investigation, including molecular testing for *PDHA1* mutations. Early diagnosis is important to facilitate supportive treatment and counseling for affected patients and their caregivers.

Abbreviations

MR	Magnetic Resonance
PDH	Pyruvate Dehydrogenase
PDHA1	Pyruvate Dehydrogenase E1 alpha gene

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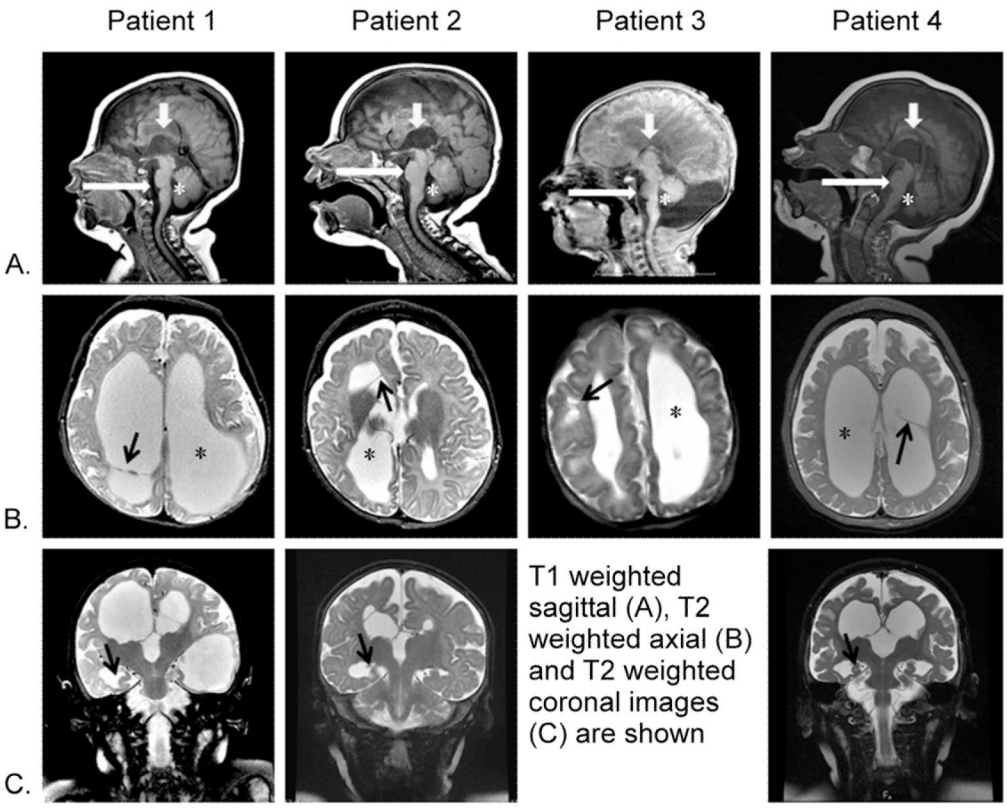

Figure 1. MRI characteristics in 4 female patients with *PDHA1* deficiency

Columns show patients 1, 2, 3, and 4 imaged at 4 months, 5 months, 1 day, and 11 months, respectively. Rows: A, sagittal midline T1-weighted images; B, axial T2-weighted images at the level of lateral ventricles; C, coronal T2-weighted images through the hippocampi. Note the incomplete corpus callosum in all patients (Row A, short white arrows). All patients had asymmetrical ventriculomegaly (Row B, stars) with a normal 4^{th} ventricle (Row A, stars). A small pons (Row A, long white arrows) can be seen. Ventricular septations were seen in 3/4 patients (row B, patients 1,2 and 4, black arrows) or parenchymal cysts in 1/4 patients (row B, patient 3, black arrow). Patients 1,2 and 4 displayed hyporotated hippocampi (row C, arrows).