Novel imaging findings in pyruvate dehydrogenase complex (PDHc) deficiency—Results from a nationwide population-based study

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Abstract
The vast clinical and radiological spectrum of pyruvate dehydrogenase complex (PDHc) deficiency continues to pose challenges both in diagnostics and disease monitoring. Prompt diagnosis is important to enable early initiation of ketogenic diet. The patients were recruited from an ongoing population-based study in Sweden. All patients with a genetically confirmed diagnosis who had been investigated with an MRI of the brain were included. Repeated investigations were assessed to study the evolution of the MRI changes. Sixty-two MRI investigations had been performed in 34 patients (23 females). The genetic cause was mutations in PDHA1 in 29, PDHX and DLAT in 2 each, and PDHB in 1. The lesions were prenatal developmental in 16, prenatal clastic in 18, and postnatal clastic in 15 individuals. Leigh-like lesions with predominant involvement of globus pallidus were present in 12, while leukoencephalopathy was present in 6 and stroke-like lesions in 3 individuals. A combination of prenatal developmental and clastic lesions was present in 15 individuals. In addition, one male with PDHA1 also had postnatal clastic lesions. The most common lesions found in our study were agenesis or hypoplasia of corpus callosum, ventriculomegaly, or Leigh-like lesions. Furthermore, we describe a broad spectrum of other MRI changes that include leukoencephalopathy and stroke-like lesions. We argue that a novel important clue, suggesting the possibility of PDHc deficiency on MRI scans, is the simultaneous presence of multiple lesions on MRI that have occurred during different phases of brain development.

Keywords
pyruvate dehydrogenase complex deficiency, magnetic resonance imaging, stroke-like lesions, leukoencephalopathy, Leigh-like lesions.
1 | INTRODUCTION

The pyruvate dehydrogenase complex (PDHc) is a multifunctional enzyme complex in the mitochondria that converts pyruvate, the end product of glycolysis to acetyl-CoA, which in turn enters the Krebs cycle and enables aerobic energy production. The PDHc is composed of four subcomplexes: pyruvate dehydrogenase (E1), dihydrolipoamide acetyltransferase (E2), dihydrolipoamide dehydrogenase (E3), and E3-binding protein (E3BP also known as PDH protein X). In PDHc deficiency, pyruvate is instead metabolized to lactate, leading to impaired production of energy through the mitochondrial respiratory chain. The brain is especially susceptible to this metabolic alteration, as glucose is the obligatory pathway for energy production under normal conditions. Consequently, PDHc deficiency predominantly affects the central nervous system. Alternative substrates to glucose in the brain are ketone bodies, and it has been demonstrated that ketogenic diet is an effective and safe treatment in most patients with the disorder. There are six known genes associated with primary PDHc deficiency: PDHA1, PDHB, PDHX, DLAT, DLD, and PDP1, where the first one is the most common, accounting for up to 90% of all known mutations.

PDHc deficiency has a large phenotypical variation ranging from neonatal encephalopathy with lactic acidosis to nonprogressive infantile encephalopathy, Leigh syndrome, and relapsing ataxia. The brain lesions have been attributed to two main mechanisms: (a) low energy supply during embryonic development resulting in agenesis of the corpus callosum or abnormalities of cortical gyration, and (b) acute energy failure either prenatally resulting in ventriculomegaly and periventricular cysts or postnatally causing acute basal ganglia or brainstem lesions.

There are few research studies exploring the MRI phenotypes in PDHc deficiency, with the existing knowledge originating mainly from case reports and smaller case series. Ventriculomegaly is the most frequent MRI finding, ranging from 35% to 85% in different cohorts. Hypoplasia or agenesis of the corpus callosum is found in over one-third of patients with PDHc deficiency, the vast clinical and radiological spectrum of the disease continues to pose challenges both in diagnostics and disease monitoring. Prompt diagnosis is important to enable early initiation of treatment. The aim of this nationwide population-based study was to delineate the neuroradiological spectrum of PDHc deficiency and its evolution over time.

2 | METHODS

2.1 | Patients

In an ongoing population-based Swedish study of PDHc deficiency, we identified 34 patients who had been investigated with MRI scans of the brain. The patients were identified from registries at the two national metabolic centers and by contacting genetics, pediatrics, and neurology departments in the country. The patients were diagnosed between 1 January 1996 and 31 December 2019. The genetic cause was determined in all the patients, with mutations in PDHA1 in 29 patients, PDHX in 2, DLAT in 2, and PDHB in 1 patient (Figure 1). There were 11 males and 23 females. Two of them were related, a mother and daughter. Repeated MRI investigations had been performed in 16 patients, and in total, there were 62 MRI investigations.

2.2 | MRI investigations

The MRI examinations were performed at eight Swedish hospitals, either for diagnostic purposes or as part of the patient evaluation, sometimes during an acute deterioration. The examinations were carried out using a 1-Tesla magnet in two patients and 1.5-Tesla or 3-Tesla magnets in the remaining patients. The examinations consisted of sagittal spin echo (SE) T1, axial fast SE T2 in all patients; coronal fluid attenuated inversion recovery (FLAIR)
images in 25 patients and diffusion-weighted images (DWI) with apparent diffusion coefficient (ADC) in 26 patients. Magnetic resonance spectroscopy (MRS) was performed in 13 patients. It was performed in the basal ganglia in all patients and in the deep white matter and cortex in occasional patients. Additional imaging sequences were occasionally obtained, including T1 with contrast, gradient echo T2, diffusion tensor imaging, proton density imaging, 3D time-of-flight angiography, and fast imaging employing steady-state acquisition.

2.3 | Study design

The MRI investigations were reevaluated by a child neuroradiologist (LI) who was blinded to the patients' phenotypes, and a pediatric neurologist (AS), using a standardized evaluation form. The patients were then subdivided into those with prenatal lesions of developmental or clastic origin and those with postnatal lesions due to suspected acute energy failure. In the patients with repeat examinations, the evolution of the imaging findings was evaluated separately for each patient and was related to significant clinical incidents and treatment. Each follow-up examination was compared to the preceding one, and the abnormalities were systematically classified as stable (no changes detected on DWI or T2 sequences), progression (new lesions present or number and/or extension of previously visualized lesions had increased), regression (complete resolution on both DWI and T2 images of lesions, previously visible), or evolution (normalization of DWI with persistent T2 changes or decreased size of the T2 signal changes as a result of encephalomalacia/atrophy).15 We report the first abnormal MRI in all but two patients while MRS was reported if abnormal at any time. For patient #24 and #26, a later MRI that was more representative than the first one is reported, even if the first one was also abnormal.

2.4 | Terminology

The categorization used to describe the extent of the lesions was trichotomized into mild, moderate, or severe. A prenatal developmental lesion was considered in the presence of agenesis or hypoplasia of corpus callosum, abnormal cortical gyration, or gray matter heterotopias. A prenatal clastic lesion was considered in the presence of ventriculomegaly, considered to be of prenatal origin, ventricular membranes, periventricular cysts, or periventricular high T2 signal suggesting gliosis. A postnatal lesion was considered in patients with increased T2 signal, reduced diffusion, or presence of edema suggesting ongoing damage not related to gliosis. Bilateral symmetrical lesions detected in basal ganglia and/or thalamus.
| ID/sex  | Age first signs/ MRI clinical signs motivating MRI | Cerebral cortex | Supratentorial white matter | Corpus callosum | Ventricles (ventriculomegaly/membranes) | Basal ganglia/thalamus/brainstem | Cerebellum | MRS | Gene |
|---------|--------------------------------------------------|----------------|-----------------------------|----------------|----------------------------------------|---------------------------------|------------|-----|------|
| 1/F     | Birth/0 y 1 mo Hypotonia, FTT                    | Mild widening of sulci | Vasogenic edema R, atrophy | Partial agenesis, hypoplasia | Moderate R, mild L/bilateral membranes | ↓ volume basal ganglia, thalamus | Normal    | n/a | PDHA1 |
| 2/F     | Birth/1 y 2 mo SGA, lactic acidosis              | Severe widening of sulci abnormal gyration | Atrophy | Total agenesis | Moderate R, severe L/bilateral membranes | ↓ volume basal ganglia, thalamus, midbrain, pons | Normal    | n/a | PDHA1 |
| 3/F     | Birth/1 y 8 mo Hypotonia, FTT                    | Mild widening of sulci | Atrophy | Hypoplasia | Moderate bilateral/bilateral membranes | ↓ volume pons | Normal    | n/a | PDHA1 |
| 4/F     | Birth/1 y 0 mo Hypotonia                         | Mild widening of sulci subdural hematoma | Delayed myelination, atrophy, periv. heterotopias | Normal | Mild L/unilateral membranes | Normal | Normal    | ↓ NAA | PDHA1 |
| 5/F     | Birth/0 y 1.5 mo SGA, hypotonia, lactic acidosis | Mild widening of sulci | Atrophy | Total agenesis | Mild R, moderate L | ↓ volume basal ganglia, thalamus | Normal    | n/a | PDHA1 |
| 6/F     | Birth/1 y 0 m Microcephaly                       | Mild widening of sulci | Periv. cyst | Partial agenesis | Mild bilateral/unilateral membrane | Normal | Normal    | n/a | PDHA1 |
| 7/F     | Birth/0 y 0 m Hypotonia, lactic acidosis         | Swelling | Generalized vasogenic edema, swollen | Partial agenesis | Moderate bilateral/bilateral membranes | ↓ volume, ↑ T2 basal ganglia | Normal    | n/a | PDHA1 |
| 8/F     | Birth/2 y 3 mo Microcephaly, psychomotor delay   | Normal | Delayed myelination, atrophy | Partial agenesis | Mild bilateral, more L/bilateral membranes | Normal | Normal    | ↓ NAA, ↓ choline | PDHA1 |
| 9/F     | Birth/0 y 0 mo SGA, hypotonia, lactic acidosis   | Normal | Generalized vasogenic edema, atrophy | Total agenesis | Moderate bilateral | ↓ volume basal ganglia, thalamus | ↑ subarachnoidal space post. fossa | n/a | PDHA1 |
| 10/F    | 1 wk/16 y 1 mo Seizures                         | Moderate widening of sulci, abnormal gyration | Atrophy | Hypoplasia | Mild R, moderate L/bilateral membranes | ↓ volume basal ganglia, thalamus | ↑ subarachnoidal space post. Fossa | ↑ lactate | PDHA1 |

(Continues)
| ID/sex | Age first signs/ MRI clinical signs motivating MRI | Cerebral cortex | Supratentorial white matter | Corpus callosum | Ventricles (ventriculomegaly/ membranes) | Basal ganglia/thalamus/ brainstem | Cerebellum | MRS | Gene  |
|---------|--------------------------------------------------|----------------|----------------------------|-----------------|------------------------------------------|---------------------------------|-------------|------|-------|
| 11/F    | 1 wk/0 y 7 m FTT, seizures                       | Moderate widening of sulci | Delayed myelination, atrophy | Partial agenesis, hypoplasia | Moderate bilateral/ bilateral membranes | Normal | Normal | n/a | PDHA1 |
| 12/F    | 3 w/0 y 8 mo Seizures                           | Severe widening of sulci  | Atrophy                     | Hypoplasia       | Moderate bilateral                        | Normal | Normal | n/a | PDHA1 |
| 13/F    | 2 mo/0 y 11 mo FTT                              | Mild widening of sulci, subarachnoid cyst | Atrophy | Normal | Moderate R, mild L                      | Normal | Normal | n/a | PDHA1 |
| 14/F    | <3 mo/0 y 8 mo Psychomotor delay                 | Moderate widening of sulci | Atrophy                     | Hypoplasia       | Moderate R, mild L/unilateral membranes  | Normal | Normal | n/a | PDHA1 |
| 15/F    | 3 mo/1 y 3 mo Hypotonia, ataxia                  | Normal | | ↑ T2, atrophy periv. | Hypoplasia       | Normal | Normal | Normal | Normal | PDHA1 |
| 16/F    | 1 y 6 mo/13 y 9 mo Psychomotor delay             | Normal | | ↑ T2 periv.       | Normal           | Normal | Normal | Normal | n/a    | PDHA1 |
| 17/M    | Birth/0 y 0 mo SGA, hypotonia                    | Abnormal gyration        | Generalized cytotoxic edema, periv. cysts | Total agenesis | Mild bilateral/ unilateral membrane | Normal | ↑ T2 white matter | ↑ lactate | PDHA1 |
| 18/M    | 11 mo/1 y 3 mo Ataxia, intermittent nystagmus    | Normal | | ↑ T2 periv.       | Normal           | Normal | Normal | Normal | n/a    | PDHA1 |
| 19/F    | Birth/1 y 11 mo SGA, hypotonia                   | Normal | | Delayed myelination, atrophy | Partial agenesis | Normal | Normal | Normal | n/a    | PDHX  |

Abbreviations: ↑, Increased; ↓, reduced; F, female; FTT, failure to thrive; L, left; M, male; MRS, magnetic resonance spectroscopy; n/a, not available; periv., periventricular; post., posterior; R, right; SGA, small for gestational age; NAA, N-acetylaspartate.
and/or brain stem with hyperintense signal on T2-weighted and variable signal on T1-weighted imaging suggested Leigh syndrome. Leukoencephalopathy was considered if the images showed hyperintensities of the cerebral white matter in T2-weighted images with swelling, with or without diffusion changes. Reduced volume was the term used when the volume was reduced compared to what was expected for age. Atrophy was used when the volume was reduced compared to the previous radiological images. Cortical atrophy was characterized by the presence of cortical thinning leading to enlarged cortical sulci. Abnormalities of the corpus callosum were classified as follows: total agenesis, when totally absent; partial agenesis when there was absence of

FIGURE 2  Patient 7, female with PDHA1. At 4 days of age (A) axial and (B) coronal T2 (1.5 T, TR/TE = 3000/103.52 ms) demonstrate swollen white matter (*), ventriculomegaly, intraventricular membranes (A arrow) and periventricular cysts (B arrows). At 2 years 1 month of age (C) axial T2 (1.5 T, TR/TE = 3161.0/95.26 ms), demonstrates white-matter atrophy, while (D) coronal T2 FLAIR (1.5 T, TR/TE = 10000/148.36 ms) demonstrates high T2 signal in white matter (arrows). Patient 9, female with PDHA1. At 1 week of age, (E) axial T2 (3T, TR/TE = 3000/80 ms) demonstrates ventriculomegaly, white-matter atrophy and PVL-like changes. At the age of 2 weeks, (F) axial T2 (1.5 T, TR/TE = 5000/100 ms) demonstrates multiple strokes (arrows). At the age of 1 month, (G) axial T2 (1.5 T, TR/TE = 5000/100 ms) demonstrates multicystic encephalopathy, while (H) sagittal FIESTA (1.5 T, TR/TE = 1500/250 ms) demonstrates corpus callosum agenesis. Patient 17, male with PDHA1. At 5 days of age, (I) axial and (J) coronal T2 (1.5 T, TR = 8070 ms, TE = 93 ms) demonstrates total corpus callosum agenesis, swollen white matter (*), ventriculomegaly, and intraventricular membrane (arrow), (K) DWI demonstrates increased diffusion (arrows) and (L) demonstrates reduction in the ADC (1.5 T, TR = 7423 ms, TE = 120 ms) compatible with cytotoxic white-matter edema. ADC, Apparent diffusion coefficient; FIESTA, fast imaging employing steady-state acquisition; FLAIR, fluid attenuated inversion recovery; TR, time repetition; TE, time to echo.
| Sex  | Age first signs/ MRI Clinical signs promoting MRI | Cortex | Supratentorial white matter | Corpus callosum | Ventricles (ventriculomegaly/membranes) | Basal ganglia/thalamus/brainstem | Cerebellum | MRS | Gene |
|------|--------------------------------------------------|--------|-----------------------------|-----------------|----------------------------------------|---------------------------------|------------|-----|------|
| 20/F | Birth/4 y 0 mo Hypotonia, FTT                   | Normal | Normal                       | Normal          | Normal                                  | Normal                          | Normal     | lactate | PDHA1 |
| 21/F | 1 mo/1 mo Seizures, hemiparesis L               | Cytotoxic edema R | ↓ diffusion whole hemisphere R | ↓ diffusion     | Normal                                  | Normal                          | n/a        | PDHA1 |
| 22/F | 1 y 0 mo/4 y 7 mo Psychomotor delay, episodic ataxia | Normal | ↑ T2                         | Normal          | Normal                                  | Vasogenic edema basal ganglia   | ↑ T2 gray matter, swollen       | NAA       | choline |
| 23/F | 8 y/27 y 6 mo Epilepsy, polyneuropathy          | Normal | Normal                       | Normal          | ↑ T2, atrophy basal ganglia             | Normal                          | n/a        | PDHA1 |
| 24/M | Birth/1 y 8 mo SGA, lactic acidosis             | ↑ diffusion bilateral, mild widening of sulci | Generalized cytotoxic edema, swollen | Normal         | Mild bilateral                          | ↑ diffusion basal ganglia, diffusion midbrain, pons, medulla oblongata | Normal     | NAA | lactate |
| 25/M | Birth/4 d Hypotonia, seizures, FTT              | Normal | Generalized vasogenic edema, swollen | Vasogenic edema | Normal                                  | ↑ diffusion, swollen basal ganglia, swollen thalamus, diffusion, swollen midbrain, pons, medulla oblongata | ↑ T2 white matter, dentate nucleus | n/a | PDHA1 |
| 26/M | 2 mo/3 y 4 mo Seizures                          | Normal | Atrophy deep (normal at age 5 mo) | Atrophy         | Mild bilateral                          | ↑ T2 basal ganglia, T2 midbrain | Atrophy (normal at age 5 mo)    | NAA       | PDHA1 |
| 27/M | <6 mo/2 y 3 mo Psychomotor delay, episodic weakness | Normal | ↑ T2 posterior horns          | Normal          | Normal                                  | ↑ T2 basal ganglia              | Normal     | n/a | PDHA1 |
| 28/M | 8 mo/8 mo Hypotonia, lactic acidosis            | Normal | Normal                       | Normal          | Mild bilateral                          | ↑ T2 basal ganglia              | Normal     | n/a | PDHA1 |
at least one, but not all, of the anatomically defined regions of corpus callosum; and hypoplasia when the corpus callosum was thinner than expected but with normal anterior-posterior extent. Myelination was characterized as normal, if normal compared to age-matched healthy individuals. Delayed myelination was defined as a substantial deficit in myelin deposition in the brain, with “catch-up” if it was first delayed but was normal on follow-up. Hypomyelination was defined as permanent myelin deficiency in the brain, as demonstrated in a follow-up MRI while dysmyelination was defined as a substantially reduced myelin deposition in the brain, as characterized by a signal change in white matter on diffusion weighted images. T2 signal was considered when it appeared bright on DWI and dark on ADC.

### RESULTS

We identified three patients with normal MRIs of the brain, all with postnatal onset. One male with PDHA1-related disease experienced intermittent ataxia and epilepsy at the age of 3 years and 8 months. The MRI was performed at the same age. Another male with DLAT-related disease experienced ataxia and dysarthria at the age of 2 years and 4 months. The MRI was performed 6 months later. One female with PDHA1-related disease had psychomotor delay from the age of 6 months and normal MRIs at the ages of 3 and 6 years.

### Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethical Review Board at Gothenburg university. Oral and written consents were obtained by the patients and/or their legal guardians before undertaking any study-related procedures.

### Table 2 (Continued)

| Sex | Age first signs/ MRI Clinical signs promoting MRI | Cortex | Supratentorial white matter | Corpus callosum | Ventricles (ventriculomegaly/ membranes) | Basal ganglia/ thalamus/brainstem | Cerbellum | MRS | Gene |
|-----|--------------------------------------------------|--------|-----------------------------|-----------------|------------------------------------------|--------------------------------|-----------|-----|------|
| 29/F | 1 y 0 mo/1 y 0 mo Hypotonia, ataxia | Normal | Normal | Normal | T2 posterior horns | Normal | T2 medulla oblongata | T2 dentate nucleus | n/a | PDHB |
| 30/M | Birth/20 d Seizures, lactic acidosis | Normal | Generalized vasogenic edema, swollen | Normal | Normal | Normal | T2 medulla oblongata | T2 dentate nucleus | NAA | PDHX |
| 31/M | Birth/4 y 11 mo SGA, ataxia, dystonia | Normal | Normal | Normal | Normal | Normal | T2 basal ganglia diffusion basal ganglia | Normal | NAA | choline |

### Abbreviations:

| Abbreviation | Meaning |
|--------------|---------|
| T2           | T2-weighted images |
| DWI          | Diffusion weighted images |
| ADC          | Apparent diffusion coefficient |
| MRS          | Magnetic resonance spectroscopy |
| n/a          | Not available |
| F            | Female |
| M            | Male |
| R            | Right |
| L            | Left |
| SGA          | Small for gestational age |
| NAA          | N-acetylaspartate |
| PDHB         | Peroxisome proliferator activator receptor beta/ delta |
| PDHX         | Peroxisome proliferator activator receptor gamma |
| DLAT         | Defect in lysosomal acid lipase activity |

Developmental abnormalities of the brain were present in 14/16 females: with corpus callosum agenesis or hypoplasia in 13; cortical gyration abnormalities in 2; reduced regions of corpus callosum; and hypoplasia when the corpus callosum was thinner than expected but with normal anterior-posterior extent. Myelination was characterized as normal, if normal compared to age-matched healthy individuals. Delayed myelination was defined as a substantial deficit in myelin deposition in the brain, as demonstrated in a follow-up MRI while dysmyelination was defined as a substantially reduced myelin deposition in the brain, as characterized by a signal change in white matter on diffusion weighted images. T2 signal was considered when it appeared bright on DWI and dark on ADC.
The myelination was delayed in three of them. Suspected prenatal clastic lesions were in addition identified in 13/14 of the females with developmental abnormalities, with ventriculomegaly in all and ventricular membranes in 10/14. The ventricular membranes were always associated with ventriculomegaly. Periventricular cysts were present in one of the patients. In two of the females (7 and 9) with developmental and prenatal clastic lesions, additional postnatal lesions were also noted with generalized vasogenic edema in the supratentorial white matter (Figure 2A-H). Suspected prenatal clastic lesions without signs of developmental abnormalities or postnatal lesions were present in two of the females (13 and 16). Widening of the sulci was identified in 11/16 of the females with PDHA1-related disease and was predominantly located to the frontotemporal area in six of them. It was always associated with ventriculomegaly. Supratentorial white-matter atrophy was present in 13/16, in 1 female without relationship to either ventriculomegaly or abnormalities in corpus callosum. One male (17) with a hemizygous PDHA1 mutation had lesions considered to be prenatal developmental as well as pre- and postnatal clastic. The postnatal clastic lesion consisted of generalized cytotoxic edema in supratentorial and cerebellar white matter (Figure 2I-L). One male (18) with hemizygous PDHA1 mutation had isolated increased T2 signal in periventricular white matter. The MRI of the brain in the patient with PDHX-related disease (19) demonstrated partial agenesis of corpus callosum and delayed myelination and atrophy of supratentorial white matter. In total, ventriculomegaly was present in 15/19 patients and was asymmetric in eight.

3.2 MRI changes in patients with postnatal disease onset

Clinical onset was considered postnatal in 15 patients. The 12 patients with abnormal MRI findings are included in Table 2. PDHA1-related disease was the cause in nine of them (four females). Stroke-like lesions were detected in two of them. Patient 21 had seizures and left-side
| Sex | Clinical signs/age at onset | (Age)/initial MRI | (Age)/new symptoms/treatment | (Age)/repeat MRI | (Age)/new symptoms/treatment | (Age)/repeat MRI | Genetics/outcome |
|-----|-----------------------------|-------------------|-----------------------------|-----------------|-----------------------------|-----------------|----------------|
| 1/F | Hypotonia, FTT/birth        | (1 mo) T2, mild widening of sulci cerebral cortex, abnormal gyration R, T2, atrophy STWM, CC partial agenesis, hypoplasia, ventriculomegaly moderate R, mild L membranes, ▼ volume R nucleus caudatus, thalamus | (0 y 10 mo) Infantile spasms Intermittent vomiting | (1 y) Progression: Progress T2 cerebral cortex and STWM, more atrophy STWM, and cortex | (3 y 9 mo) K.D | (5 y 1 mo) Stable: No changes | PDHA1 Alive |
| 3/F | Hypotonia, FTT/birth        | (1 y 8 mo) mild widening sulci cerebral cortex, moderate STWM atrophy bilateral, CC hypoplasia, moderate ventriculomegaly and bilateral membranes, ▼ volume pons | | (3 y 1 mo) Stable: No changes | (14 y 5 mo) K.D | | PDHA1 Alive |
| 4/F | Hypotonia/birth             | (1 y 0 mo) mild widening of sulci cerebral cortex, subdural hematoma, atrophy STWM, heterotopias, ▼ myelination Mild ventriculomegaly L, unilateral membranes | (1 y 7 mo) K.D | (2 y 5 mo) Evolution: T2 deep STWM with catch up myelination | | | PDHA1 Alive |
| 6/F | Microcephaly, psychomotor delay, FTT/birth | (1 y 0 mo) mild widening of sulci cerebral cortex, periventricular cyst, posterior CC agenesis, symmetrical ventriculomegaly, unilateral ventricular membranes | (3 y 10 mo) Evolution: STWM atrophy left, asymmetrical ventriculomegaly more left | (7 y 7 mo) K.D | | | PDHA1 Alive |
| 7/F | Hypotonia, lactic acidosis/birth | (4 d) swollen cerebral cortex, T2 STWM, CC partial agenesis and hypoplasia, moderate ventriculomegaly, bilateral membranes, ▼ volume nuclei caudati bilateral, T2 globus pallidus L | (1 mo) K.D | (2 y 1 mo) Evolution: Atrophy STWM, cystic degeneration | (2 y 8 mo) Stable: No changes | | PDHA1 Alive |
| 9/F | SGA, hypotonia, lactic acidosis/birth | (1 wk) atrophy STWM, CC agenesis, moderate ventriculomegaly, ▼ volume basal ganglia, thalamus | (2 wk) Progression: Patchy T2 and edema cerebral cortex | (2 wk) K.D | (1 mo) Evolution: Cystic degeneration | | PDHA1 Alive |
| 12/F | Seizures/3 wk               | (0 y 8 mo) severe widening sulci cerebral cortex, atrophy STWM, CC hypoplasia, moderate ventriculomegaly | (10 y 1 mo) Thiamin | (11 y 10 mo) Evolution: T2 STWM | (14 y 8 mo, 17 y 8 mo) Stable: No changes | | PDHA1 Alive |

(Continues)
| Sex | Clinical signs/age at onset | (Age)/initial MRI | (Age)/new symptoms/treatment | (Age)/repeat MRI | (Age)/new symptoms/treatment | (Age)/repeat MRI | Genetics/ outcome |
|-----|-----------------------------|------------------|-----------------------------|-----------------|-----------------------------|-----------------|------------------|
| 21/F| Seizures, hemiparesis left side/1 mo | (0 y 1 mo) cytotoxic edema cerebral cortex R, ↓ diffusion STWM R, nuclei caudati, globi pallidi, thalamus, midbrain R, CC | (0 y 1.5 mo) Evolution: Evolution to atrophy of the same areas, mild ventriculomegaly R | (1 y 0 mo) K.D | | PDHA1 Alive |
| 22/F| Psychomotor delay, episodic ataxia/1 y 0 mo | (4 y 7 mo) ↑ T2 STWM, vasogenic edema basal ganglia, ↑ T2 and swollen gray matter cerebellum | (5 y 7 mo) episodic ataxia | (6 y 4 mo) Progression: New ↑ T2 cerebellar gray matter, global atrophy cerebellum | (7 y 6 mo) Episodic ataxia | (8 y 0 mo) K.D | PDHA1 Alive |
| 24/M| SGA, lactic acidosis/birth K.D 1 mo | (0 y 3.5 mo) mild widening of sulci cerebral cortex, cytotoxic edema and swollen STWM | (1 y 8 mo) Progression: New ↓ diffusion cerebral cortex, basal ganglia and mesencephalon, atrophy STWM | | | PDHA1 Dead |
| 25/M| Hypotonia, seizures, FTT/birth | (4 d) vasogenic edema STWM and CC, ↓ diffusion basal ganglia and midbrain, swollen thalamus, pons, medulla oblongata, ↑ T2 STWM cerebellum, dentate nucleus | (3 wk) Progression: ↑ T2 signal basal ganglia, midbrain, thalamus, pons, medulla oblongata, patchy cerebral cortex atrophy, widespread atrophy | (3 wk) K.D | | PDHA1 Early death |
| 26/M| Seizures/2 mo | (0 y 5 mo) delayed myelination, normal CC | (6.5 mo) K.D | (3 y 4 mo) Progression: Atrophy STWM, CC, cerebellum, new ↑ T2 basal ganglia, midbrain | | PDHA1 Alive |
| 27/M| Psychomotor delay, intermittent muscle weakness/<6 mo | (2 y 3 mo) ↑ T2 STWM, globi pallidi | (3 y 5 mo) K.D | (12 y 5 mo) Stable: No changes | | PDHA1 Alive |
| 28/M| Episodic hypotonia, lactic acidosis/8 mo | (8 mo) mild ventriculomegaly, ↑ T2 globi pallidi | (4 y 5 mo) Progression: Mild progress ↑ T2 globi pallidi | | | PDHA1 Alive |
hemiparesis at the age of 1 month with cytotoxic edema of the right hemisphere on MRI (Figure 3A-E), while the MRI in patient #22 demonstrated stroke-like lesions in cerebellum (Figure 3F-J). All but one patient with postnatal onset developed Leigh-like changes. Involvement of the basal ganglia with abnormalities in the globi pallidi was seen in all of them while involvement of putamina, nuclei caudati, and globi pallidi was seen in five patients. Involvement of the brainstem was present in four, of which two had abnormalities in midbrain, pons, and medulla oblongata and two in midbrain only. Involvement of thalamus was seen in two patients, all in combination with basal ganglia and brainstem abnormalities. Supratentorial white-matter changes were identified in eight of the patients with postnatal onset. Increased T2 signal of unspecific origin was identified in four of them. In three of the patients, there was a swollen appearance of supratentorial white matter with generalized cytotoxic (#24) or vasogenic edema (#25 and #30). Mild ventriculomegaly was seen in three of the patients, all males. Cerebellar involvement was identified in five patients with variable involvement of cortex, white matter, or nuclei dentati. The MRI in the patient with PDHB-related disease (#29) showed hyperintense T2 signal in posterior horns of the lateral ventricles, medulla oblongata, and the nuclei dentati. The MRI in the patient with DLAT-related disease showed Leigh-like lesions.

3.3 Evolution of MRI changes in patients with repeated investigations

Repeat MRI investigations were done in 17 of the patients, on 43 occasions in total (Table 3). Mutations in PDHA1 was the cause in 15 of the patients (10 females). One of the females had normal MRIs both times and is therefore not included in the table. Prenatal developmental lesions in combination with prenatal clastic lesions were found on MRI in six of nine females with PDHA1-related disease (#1, 3, 4, 6, 7, and 12). One of the females with PDHA1-related disease had a combination of prenatal developmental and clastic lesions and showed progression on MRI with additional postnatal clastic lesions with focal stroke-like lesions in cerebral cortex (#9). One female with postnatal-onset PDHA1-related disease and a stroke-like episode at 1 month of age (#21) showed evolution on follow-up. Another female with postnatal onset and Leigh syndrome (#22) showed progression and evolution between repeated investigations performed after episodes of clinical deterioration, with new lesions, including stroke-like lesions with T2 hyperintensities and focal atrophic development, but also with other lesions showing complete regression. The course in the males
with PDHA1-related disease was progressive in four of five leading to death in two of them. MRIs of the patient with PDHX-related disease (#30) showed evolution of lesions with variable white-matter involvement (Figure 4A-D) while MRI of the patient with DLAT-related disease was stable on follow-up. Repeat MRI after initiation of a ketogenic diet was performed in eight patients on 10 occasions in total and showed stabilization in three, evolution in six, and progression in one of the investigations.

4 | DISCUSSION

Even though PDHc deficiency is considered the major cause of primary lactic acidosis in children,13 most previous studies have been small, and none have systematically reviewed the neuroimaging findings in a large population-based cohort. Similar to previous studies,3,5,8 the most common lesions found in our study were agenesis or hypoplasia of corpus callosum, ventriculomegaly, or Leigh-like lesions. In addition, we describe a broader spectrum of MRI changes that include leukoencephalopathy and stroke-like lesions. An important clue from our study that should suggest the possibility of PDHc deficiency is the simultaneous presence of multiple lesions on MRI that have occurred during different phases of brain development.

The energy dependency of different neuroanatomic sites of the brain is related to the different phases of brain development. Consequently, the nature and localization of brain injury is dependent on the timing of the injury.21 Two pathophysiological mechanisms have been proposed in PDHc deficiency, either developmental or degenerative, the latter in which cell death leads to encephaloclastic lesions.22 Developmental lesions occur during the second trimester of pregnancy when neuronal proliferation, migration, and differentiation require large amounts of energy. It is also from this period that the development of the brain becomes dependent on the enzymatic activity of pyruvate dehydrogenase and pyruvate carboxylase.23 Typical developmental lesions found in neuropathological studies of PDH deficiency consist of migration anomalies, corpus callosum dysgenesis, malformed nuclei dentati, internal granular cell layer and Purkinje cell layer paucity, and abnormal and ectopic inferior olivary nuclei.24 These lesions are reminiscent of the fetal alcohol syndrome,2 in which similar pathophysiological mechanisms to PDHc deficiency could be present. Excessive intake of alcohol is associated with deficiency of thiamine, the cofactor of PDHc,25 and in addition, acetaldehyde, the product of alcohol oxidation, has been found to have an inhibitory effect on PDHc.2 The second proposed mechanism is degenerative and results from acute failure of energy supply, responsible for cell death, and leading to encephaloclastic lesions which can occur either prenatally or postnatally. Prenatal degenerative neuropathological changes in PDHc deficiency consist of a variety of lesions, including cortical and white-matter atrophy, calcified migrating neurons, subependymal pseudocysts, periventricular cavitary, and non-cavitary lesions surrounded by reactive gliosis, ventricular dilatation, and basal ganglia calcifications.24 The presence of ventricular septations may also be the result of a destructive process and may represent areas of incomplete porencephaly or cystic lesions.11 The clastic lesions in periventricular white matter and associated ventriculomegaly described in PDHc deficiency bear similarities both on neuroimaging and neuropathological studies to the hypoxic-ischemic periventricular leukomalacia/diffuse white-matter injury-like lesions typical of cerebral palsy in preterm infants.24 It is therefore important to consider PDHc deficiency in the differential diagnosis of cerebral palsy in girls with atypical perinatal history. In contrast to a previous case report that emphasized the asymmetry of ventricular dilatation in PDHc deficiency as a distinguishing
pattern, half of the patients in our study had symmetric ventricular dilatation.

Stroke-like lesions were detected in three of our patients with PDHA1-related disease. While we have not been able to find any previous study describing stroke-like episodes in PDHc deficiency, they do occur in other mitochondrial diseases, that is, POLG-related Alpers disease and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.

Five patients with PDHA1- and one with PDHX-related disease, all but one investigated in the neonatal period, had a very similar MRI pattern suggestive of leukoencephalopathy with generalized swollen appearance of supratentorial white matter due to vasogenic edema in five and cytotoxic edema in two of the patients. The different pattern of edema seen in these patients is probably reflective of the time frame of the MRI investigation in relation to the development of the underlying lesion, as brain edema could be considered as a continuum starting with cytotoxic cell swelling and ending in vasogenic edema. A suggestive clue on MRI in these patients was the additional presence of either prenatal or Leigh-like lesions. This MRI pattern is similar to a previous case report but seems otherwise underreported in PDH deficiency and was not mentioned in a comprehensive review of 371 published patients. In addition, delayed myelination was seen in four patients with prenatal onset while four patients with postnatal onset had unspecific white-matter lesions probably related to dysmyelination or gliosis. We hypothesize that the white matter could be particularly vulnerable to disturbances in the pyruvate metabolism, especially during the fetal period and first month of life. This assumption could be of interest to study further in an animal model of the disease.

All but one of the patients with postnatal onset developed Leigh-like lesions, which is the most common presentation of mitochondrial diseases in childhood. It is characterized by focal symmetrical lesions affecting the basal ganglia, diencephalon, brainstem, cerebellum, and spinal cord, typically occurring between 3 and 12 months of age when these parts of the brain are especially vulnerable to disruption in energy supply. The basal ganglia involvement in our study, with predominant involvement of the globi pallidi, is similar to previous studies and differs from what has been described in other mitochondrial diseases where the lesions more commonly involve the striatum. Early diagnosis is important as the deep gray-matter lesions could be reversible after introducing a ketogenic diet.

PDHA1 deficiency is an X-linked disorder leading to different manifestations between the sexes. In our cohort, there were more than twice as many females than males. This difference is derived from the group with prenatal onset and developmental lesions whereas the distribution between the sexes was equal in patients with postnatal onset. The reason for this difference could be explained by the fact that in affected males, severe PDHA1 mutations that essentially abrogate enzyme activity in the cells are thought to be embryonically lethal and only affected male fetuses with milder mutations, and significant residual enzyme activity is believed to survive until birth. Consequently, newborn boys with PDHA1 deficiency typically do not manifest severe structural brain anomalies at birth although this has been described occasionally (and was found in one of our patients). In female patients, random X inactivation leads to expression of either the mutant or normal allele in neuronal cells. Therefore, even severe PDHA1 mutations result in a viable female pregnancy because cells expressing the normal allele ensure fetal survival, whereas affected cells are considered nonviable, and their death has been suggested to result in developmental abnormalities of the brain. It is believed that female patients with prenatal onset PDHA1-related disease, due to severe mutations and lack of residual enzyme activity, display a nonprogressive course and that interventions such as a ketogenic diet would not be effective given the lack of responsiveness on a cellular basis. In our study, two of seven female patients with prenatal developmental and clastic lesions (#7,9) showed progression on repeated MRI’s with additional postnatal lesions. It’s therefore possible that the pathophysiological mechanism could be more of continuum and that a ketogenic diet might be effective also in girls with developmental lesions as has been previously suggested. Even though the majority of females with PDHA1 deficiency in our study had developmental abnormalities, we identified a more variable MRI phenotype than previously described with absence of developmental lesions in one of three and postnatal onset with stroke or Leigh-like lesions in one of five of the females. The MRI changes in females with postnatal onset appeared milder than in the males. The vast predominance of girls in our study differs from previous studies that have shown equal distribution between the sexes. An explanation for this difference could be better awareness and more efficient NGS tools for diagnosis in our study compared to earlier studies. Previously, the diagnosis relied solely upon enzymatic methods which could miss the diagnosis in girls due to variable tissue distribution of the enzyme deficiency. Newborn screening might be a future option to facilitate early diagnostics and treatment.

The classification into prenatal and postnatal disease onset was performed from a pragmatic perspective and should be considered as arbitrary, as the underlying disease mechanisms most likely constitute a continuum. Our cohort of patients, even though comparably large, is
probably not representative of the full disease spectrum in the general population, as there is still likely a significant underdiagnosis, both in the severe and mild end of the spectrum, making solid conclusions difficult. Another limitation of our study was its retrospective design with investigations performed using different MRI scanners and protocols. The strength of our study was that we performed a systematic reevaluation of all available MRI scans, from a comparably large, nationwide, and population-based cohort of patients. Our findings add to a better understanding of the neuroradiological spectrum of PDHc deficiency and its evolution over time, which in turn may improve timely diagnosis and enable earlier initiation of disease-modifying treatment.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

**Antri Savvidou**: Study design; data collection and analysis; data acquisition; conceptualization; writing – original draft; writing – revision; manuscript approval. **Kalliopi Sofou**: Study design; data acquisition; writing – revision; manuscript approval. **Niklas Darin**: Conceptualization; data acquisition; writing – original draft; writing – revision; manuscript approval. **Liz Ivarsson**: Data acquisition; writing – revision; manuscript approval. **Karin Naess**: Data acquisition; writing – revision; manuscript approval. **Johan Lundgren**: Data acquisition; writing – revision; manuscript approval. **Maria Dahlin**: Data acquisition; writing – revision; manuscript approval. **Deborah Frithiof**: Data acquisition; writing – revision; manuscript approval.

ANIMAL RIGHTS

This article does not contain any studies with animal subjects performed by any of the authors.

ETHICS STATEMENT

Our study complied with the ethical guidelines and was conducted in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethical Review Board at Gothenburg university (#289–17, 106-04). All procedures followed were in accordance with the ethical responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

INFORMED CONSENT

Informed consent was obtained from all patients and/or their legal guards for which identifying information is included in this article.

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