Acute Late-onset Pyruvate Dehydrogenase Deficiency with Specific Diagnostic Clues

Report of Five New Patients

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Keywords

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Abstract

The aim of this article was to explore acute late-onset pyruvate dehydrogenase complex (PDHc) deficiency, a mitochondrial disorder affecting energy metabolism. Five new cases are reported, and clinical features, genetic pathogenic variants and therapeutic strategies are described. Patients presented with intermittent episodes of ataxia and weakness. The diagnosis was based on biochemical studies and confirmed by molecular genetic analysis, which revealed pathogenic variants in the *PDHA1* gene. Treatment consisted of a ketogenic diet and vitamin supplementation, which led to a reduction in symptoms. This study highlighted the diversity of PDHc deficiency, the relevance of genetic analysis and the efficacy of personalised treatments such as ketogenic diets.

Introduction

Pyruvate dehydrogenase complex (PDHc) is an essential enzyme complex involved in mitochondrial energy metabolism, which catalyses pyruvate to acetyl-CoA and acts as a gateway to carbohydrate metabolism in mitochondria. This complex comprises three catalytic enzymes: E1 or pyruvate dehydrogenase, E2 or dihydrolipoamide transacetylase, and E3 or dihydrolipoyl dehydrogenase, along with an additional protein E3BP or E3 binding protein, formerly designated as protein X, as well as two regulatory enzymes, including pyruvate dehydrogenase kinase and pyruvate dehydrogenase phosphatase (1,2). PDHc deficiency impairs mitochondrial pyruvate oxidation. As a result, pyruvate is inefficiently metabolized and does not reach the tricarboxylic acid cycle, resulting in increased lactate production and reduced adenosine triphosphate production by the mitochondrial respiratory chain (3).

The clinical presentation is heterogeneous, with four phenotypes reported in patients with a pathogenic variant of the *PDHA1* gene (1,4,5), as follows:

- a neonatal-onset encephalopathy with lactic acidosis, facial dysmorphism, and brain malformations (corpus callosum, cortex, or both), mainly affecting female patients;
- an early infantile form with chronic and progressive neurological deterioration;
- an infantile form with the clinical and radiological features of Leigh syndrome and mild systemic acidosis;
- a childhood intermittent-relapsing or milder later-onset form with acute and transient weakness and ataxia episodes, possibly associated with high lactic acid and pyruvate levels in the blood, or peripheral neuropathy.

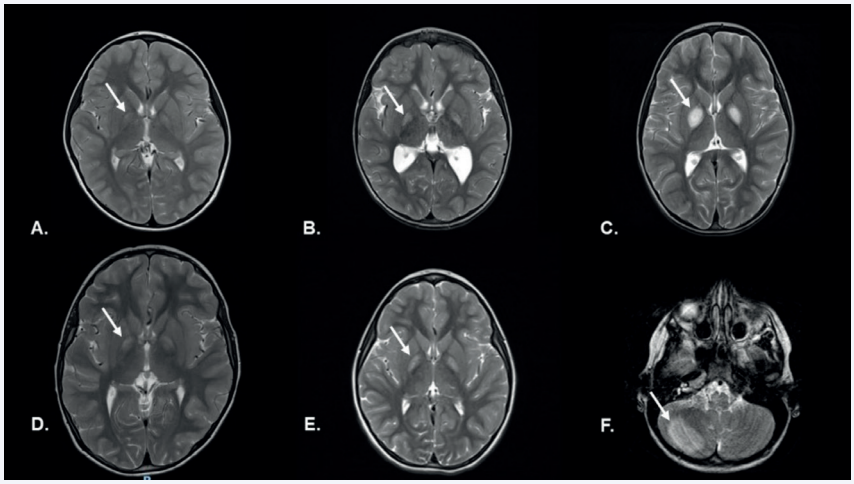
The late-onset acute form manifests as recurrent ataxia episodes and neuropathy. The first episodes can be misdiagnosed as cerebellitis or Guillain Barré syndrome (4,6).

High lactate and pyruvate levels associated with a low lactate/pyruvate ratio (<10-15) in blood and cerebrospinal fluid (CSF) are consistent indicators of PDHc deficiency. However, in milder forms, clinical and biochemical features can normalize, yet with persistent neuroradiological and electrophysiological abnormalities (5). Several genes are implicated in PDHc deficiency: the *PDHA1* (76%-85%), *PDHX* (7-11%), *PDHB* (4-9%), *DLD* (1-6%), *DLAT* (1-4%), *PDP1,* and PDK3 (each <1%) [2]. The *PDHA1* gene is located on chromosome Xp22.12. Thus, most PDHc deficiency cases are X-linked disorders. Considering the X-linked *PDHA1* gene, no known genotype-phenotype correlations were so far reported among the different pathogenic variants. Variations in severity are anticipated in female patients, given the different patterns of X-linked inactivation. However, this variability can also be observed in male patients, where it remains unexplained (7).

The ketogenetic diet is used to treat PDHc deficiency, aiming to induce ketosis, which provides an alternative source of acetyl-CoA. Thiamine is similarly used, but with limited efficacy. Thiamine responsiveness has been correlated with certain missense variants, particularly those found in exon 3 or the thiamine pyrophosphate binding site of the E1-alpha subunit (*PDHA1*), which are most receptive to treatment.

Certain treatments, such as dichloroacetate (DCA) and phenylbutyrate, function as PDHc activators. They inhibit pyruvate

FIGURE 1: Brain magnetic resonance imaging of axial T2-weighted images. A. Patient #1 at the age of five; B. Patient #2 at the age of six; C. Patient #3 at the age of six; D. Patient #4 at the age of seven; E. Patient #5 at the age of nine exhibiting bilateral and symmetric high signals of the internal part of the globi pallidi. F: Patient #5 at the age of nine presenting with a large unilateral right hemispheric cerebellar lesion.



dehydrogenase kinase 1 (PDK1), the primary inhibitor of PDHc. These therapeutic approaches are currently being investigated (NCT02616484) (8).

Methods

The aim of this paper was to report the case of five patients with acute late-onset PDHc deficiency who have been followed up over the past 10 years. Informed consent was obtained from the patients or their legal guardians.

Clinical reports

Patient #1 was a 13-year-old boy, born at term to unrelated parents. Psychomotor development was normal. At 22 months of age, he experienced intermittent ataxia and global weakness with undetectable deep tendon reflexes. A discrete bilateral diffusion restriction was detected in the globi pallidi on brain magnetic resonance imaging (MRI). Lactate levels were increased in cerebrospinal fluid (CSF), as were alanine and proline levels in plasma. Elevated lactate and pyruvate levels in blood along with the lactate/pyruvate ratio were indicative for a PDHc deficiency (Table 1). The diagnosis was confirmed by the identification of a heterozygous pathogenic variant NM_000284.4(*PDHA1*), c.262C>T, p.(Arg88Cys) in the E1alpha subunit. Thiamine and riboflavin supplementation and a ketogenic diet were implemented for 1 year, after which the ketogenic diet was discontinued and replaced by a limited sugar intake. Brain MRI performed 5 years later showed modest bilateral and symmetrical high signals in the globi pallidi (Figure 1A). At the age of 13 years, the patient showed normal psychomotor development, while following the regular education curriculum without difficulty. He did no longer experience episodes of ataxia or global weakness.

Patient #2 was a 7-year-old boy, born at term to unrelated parents. He began walking at 16 months old. His development of gross motor skills was marked by difficulties in running and frequent falls. At the age of four, he presented with falls, episodic ataxia, and fatigue persisting for several months. The clinical examination was normal except for absent deep tendon reflexes in the lower limbs. Nerve conduction velocity and electromyography were within the normal range. Brain MRI demonstrated symmetrical bilateral high T2 and FLAIR signals of the globi pallidi, with discrete diffusion restriction (Figure 1B). Elevated levels of lactate, pyruvate, and alanine were observed in the blood and CSF. The lactate/pyruvate ratios in plasma and CSF were indicative for a PDHc deficiency (Table 1). The diagnosis was confirmed by the identification of a hemizygous pathogenic variant NM_000284.4(*PDHA1*):c.214C>T, p.(Arg-72Cys) in the E1alpha subunit. Treatment involved a ketogenic diet supplemented with riboflavin and thiamine. Episodes of ataxia persisted during fever, prolonged effort, or periods of reduced diet compliance. The patient benefitted from physiotherapy and was enrolled in a regular education program.

Patient #3 was a 7-year-old boy, born at term to unrelated parents. At the age of five, the patient presented with fatigue and gait disturbances following a febrile influenza A infection. Clinical examination revealed generalized weakness and absent deep tendon reflexes, indicative of Guillain Barré syndrome. CSF analysis showed high lactate levels with normal protein levels, which did not align with the Guillain Barré syndrome. Further investigations confirmed elevated levels of lactate and pyruvate in blood and CSF, with a lactate/pyruvate ratio in blood indicative for a PDHc deficiency (Table 1). Brain MRI showed bilateral isolated discrete high T2 signals of the globi pallidi (Figure 1C). Diagnosis was confirmed by the identification of a hemizygous pathogenic variant NM_000284.4(*PDHA1*):c.262C>T, p.(Arg88Cys) in the E1alpha subunit. Treatment comprised thiamine and riboflavin supplementation, alongside a ketogenic diet, intensive physiotherapy, and occupational therapy. However, the patient continued to experience balance and endurance problems on the motor level. Additionally, as he faced learning difficulties, he is enrolled in a specialized education program.

Patient #4 was a 9-year-old boy, born at term to unrelated parents and the brother of patient #3. He has been undergoing physiotherapy since the age of four due to global hypotonia. At 7 years old, he presented with generalized weakness and balance disorders following a febrile episode. Given his brother's diagnosis, a genetic analysis was conducted, confirming the presence of the same pathogenic variant within *PDHA1* gene (E1alpha, c.262C>T). His alanine levels were increased in blood, while lactate levels were normal in urine, with slightly elevated pyruvate levels (Table 1). Brain MRI revealed a slight high T2 signal in the globi pallidi (Figure 1D). Treatment consisted of thiamine and riboflavin supplementation, along with a ketogenic diet. As the boy experienced learning difficulties, he was enrolled in a specialized education program.

Patient #5 was a 23-year-old woman, born at term to unrelated parents. She was hospitalized at the age of two due to speech loss and general weakness following a febrile illness. Guillain Barré syndrome was suspected based on her clinical presentation. Subsequently, the patient developed intermittent stiffness in her lower limbs leading to balance disorders, which were particularly exacerbated by factors like cold weather, walking, and sustained effort. Her neurological examination at 8 years old revealed absent deep tendon reflexes and bilateral tremors. Brain MRI showed bilateral high T2 signals in the globi pallidi (Figure 1E). The CSF lactate levels were increased (Table 1). Though a mitochondrial disease was initially suspected, the mitochondrial respiratory chain analysis on liver and muscle biopsies yielded normal

TABLE 1: General information, clinical and biological features, molecular genetics, and outcome

	Patient #1 (male)	Patient #2 (male)	Patient #3 (male)	Patient #4 (male)	Patient #5 (female)
General Information					
Origin	Armenia	Belgium	Belgium	Belgium	Belgium
Age of onset	22 M	4 Y	5 Y 2 M	7 Y 3 M	2 Y 4 M
Age at diagnosis	23 M	5 Y	5 Y 2 M	7 Y 3 M	14 Y
Actual age	13 Y 3 M	7 Y 10 M	7 Y 6 M	9 Y 1 M	23 Y
Neurological features					
Triggers	-	sustained physical effort	fever	fever	fever, sustained physical effort
First symptoms	falls	ataxia, falls	ataxia, falls, weakness	weakness, ataxia	weakness, ataxia, falls
Early development	nl	motor delay	speech delay	speech delay	nl
Ataxia	paroxysmal	paroxysmal	+	paroxysmal	paroxysmal
Deep tendon reflexes	absent	absent	absent	absent	absent
Dystonia	-	paroxysmal	-	-	paroxysmal
Endurance	nl	weak	weak	nl	weak
Hemiplegia/paresis	-	-	-	-	Paroxysmal
Brain MRI					
Cerebellar hyperintensity	-	-	-	-	+
Globus pallidus involvement	+	+	+	+	+
Biochemical features					
Blood					
Lactic acid (0.4 -1.8mmol/L)	7.9	2.8	3.2	ND	1.58
Pyruvate (0.03-0.10mmol/L)	0.55	0.2	ND	ND	0,19
Lactic acid/pyruvate (<15)	14,4	14.2	ND	ND	/
Alanine (144-314µmol/L)	1120	644	954	326	622
Proline (53-201µmol/L)	367	364	349	160	318
CSF					
Lactic acid (1.1-1.7mmol/L)	4.6	9.06	6.59	ND	3.2
Pyruvate	ND	0.91	0.66	ND	ND
Lactic acid/Pyruvate (<15)	ND	10	10	ND	ND
Alanine (12-34 µmol/L)	ND	92	ND	ND	43
Urines					
Lactic acid (<50mmol/mol creatine)	2546	1247	2821	<50	205
Pyruvate (<20mmol/mol creatine)	ND	151	619	33	25
Treatment					
Thiamine (B1)	+	+	+	+	+
Ketogenic Diet	limited sugar intake	modified Atkins diet	modified Atkins diet	modified Atkins diet	modified Atkins diet
Outcome					
Motor skills	Normal	Weak endurance	Weak endurance	Normal	Normal
Relapse	-	+	+	-	+
Rehabilitation	-	Physiotherapy	Speech therapy, Physiotherapy	Speech therapy, Physiotherapy	Physiotherapy
Education	Regular school	Regular school	Specialized school	Specialized school	Non-university graduate education

Y: years; M: months; NI: normal; ND: not done; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid

results. At 9 years old, she experienced further balance issues and generalized weakness. Brain MRI demonstrated a large cerebellar lesion in addition to known lesions in the globi pallidi (Figure 1F). Thiamine and riboflavin treatment was initiated as was physical therapy. By the age of 13 years, metabolic investigations revealed elevated alanine levels in blood, in association with high lactate and pyruvate levels in urine (Table 1). Genetic analysis identified a heterozygous pathogenic variant NM_000284.4(*PDHA1*):c787C>G, p.(Arg263Gly) in the E1alpha subunit. A ketogenic diet was implemented but discontinued after 4 years. While the patient continued to experience intermittent muscle cramps, she was able to pursue a non-university graduate course.

Discussion

PDHc deficiency exhibits a heterogeneous presentation manifesting across a spectrum of clinical phenotypes. One such phenotype is the childhood intermittent-relapsing or milder later-onset form with acute and transient episodes. We have described the findings from five patients whose initial symptoms first appeared between the age of 22 months and 7 years and 3 months of age, triggered by fever or prolonged physical effort. Neurological manifestations mainly comprised ataxia, falls, generalized weakness, and absent deep tendon reflexes (Table 1).

In all patients, the brain MRI displayed high T2 signals of the internal part of the globi pallidi. Several inborn metabolism errors can induce basal ganglion lesions (9). Globi pallidi involvement has been linked with respiratory chain disorders, mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D), cerebrotendinous xanthomatosis, methylmalonic aciduria, succinic semialdehyde dehydrogenase deficiency, urea cycle disorders, and metal storage disorders, such as Wilson disease, hypermanganesemia, and certain neurodegeneration forms with cerebral iron accumulation (NBIA), due to mutations in genes like WD repeat domain 45 *(WDR45)*, pantothenate kinase 2 *(PANK2)* and phospholipase A2 group VI *(PLA2G6)*.

All patients exhibited elevated lactate levels in blood or CSF when analyses were done. Additionally, four of the five patients displayed increased urinary lactate levels. The lactate/pyruvate ratios, which were examined in either CSF or plasma in three of the patients, were indicative for a PDHc deficiency. Other biological indicators consisted of increased alanine and proline levels (Table 1). Outside of acute episodes, the analyses performed in patients #4 and #5 were likely normal. PDHc deficiencies induce conversion of pyruvate into alanine and lactate rather than into acetyl-coA, the latter being essential for complete carbohydrate oxidation via the Krebs cycle. An increase in plasma proline is observed given the inhibition of proline oxidase, the first enzyme in the proline degradation pathway, in context of acquired and genetic lactic acidosis. The primary laboratory test for detecting PDHc deficiency involves measuring lactate and pyruvate levels in both blood and CSF. It is crucial to analyse lactate level in CSF in cases where Guillain Barré syndrome or acute ataxia is suspected without a clear diagnosis. Additionally, quantitative analysis of urinary organic acids and amino acids in both blood and CSF may facilitate the diagnosis.

The clinical diagnosis was confirmed by molecular genetic analysis, revealing a pathogenic variant in the E1α subunit of the *PDHA1* gene in all five patients. Three of them were found to be hemizygous for the pathogenic variant NM_000284.4*(PDHA1)*:c.262C>T, p.(Arg88Cys). The other alterations included a heterozygous pathogenic variant NM_000284.4*(PDHA1)*:c.214C>T, p.(Arg72Cys) and a heterozygous NM_000284.4(*PDHA1)*:c787C>G, p.(Arg263Gly). Notably, all variants identified in our patients were previously published in the literature.

Patient management relied on implementing a ketogenic diet, which effectively alleviated symptoms. In addition, vitamins, mainly thiamine and riboflavin, were prescribed. These vitamins are given to enhance the mitochondrial function (10). The effect of thiamine has been reported in some patients with PDH deficiency, with a reduction in blood lactate and apparent clinical improvement (9). The role of riboflavin is less reported and may be questionable. The ketogenic diet reduced the symptoms of all patients, with relapses in patient #2 due to a reduced diet compliance and in patient #5 following diet cessation. Oxidation of fatty acids and ketone bodies like acetoacetate and 3-hydroxybutyrate provided alternative acetyl-CoA sources. This diet has been associated with favourable outcomes in some patients, as manifested by a better prognosis (9,11). Their evolution was characterized by participation in regular education programs and in a special program for two patients, with or without paramedical support, such as speech therapy and physiotherapy.

In conclusion, we have herein presented five patients with pyruvate dehydrogenase deficiency exhibiting a childhood intermittent-relapsing or milder later-onset form characterized by acute and transient episodes of weakness and ataxia. Symptoms were intermittent and related to triggers, such as fever and sustained effort. A predominant biological indicator consisted of increased CSF lactate levels. Brain MRI showed high T2 signals in the globi pallidi. Molecular genetic analyses identified pathogenic variants in the *PDHA1* gene. Treatment with ketogenic diet led to symptom reduction. As aforementioned, sampling and imaging must be performed during acute episodes in order to avoid false negatives and delay management (5).

Conflict of interest. The authors have no conflict of interest to declare that are relevant to the content of this article

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