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Case Report

Pyruvate carboxylase deficiency: An underestimated cause of lactic acidosis

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ABSTRACT

Pyruvate carboxylase (PC) is a biotin-containing mitochondrial enzyme that catalyzes the conversion of pyruvate to oxaloacetate, thereby being involved in gluconeogenesis and in energy production through replenishment of the tricarboxylic acid (TCA) cycle with oxaloacetate. PC deficiency is a very rare metabolic disorder. We report on a new patient affected by the moderate form (the American type A). Diagnosis was nearly fortuitous, resulting from the revision of an initial diagnosis of mitochondrial complex IV (C IV) defect. The patient presented with severe lactic acidosis and pronounced ketonuria, associated with lethargy at age 23 months. Intellectual disability was noted at this time. Amino acids in plasma and organic acids in urine did not show patterns of interest for the diagnostic work-up. In skin fibroblasts PC showed no detectable activity whereas biotinidase activity was normal. We had previously reported another patient with the severe form of PC deficiency and we show that she also had secondary C IV deficiency in fibroblasts. Different anaplerotic treatments in vivo and in vitro were tested using fibroblasts of both patients with 2 different types of PC deficiency, type A (patient 1) and type B (patient 2). Neither clinical nor biological effects in vivo and in vitro were observed using citrate, aspartate, oxoglutarate and bezafibrate. In conclusion, this case report suggests that the moderate form of PC deficiency may be underdiagnosed and illustrates the challenges raised by energetic disorders in terms of diagnostic work-up and therapeutical strategy even in a moderate form.

1. Introduction

Pyruvate carboxylase (PC; EC: 6.4.1.1) is a biotin-containing mitochondrial enzyme composed of four functional domains: the N-terminal biotin carboxylase (BC) domain, the central carboxyl transferase (CT) domain, the tetramerization domain (PT) and the C-terminal biotin carboxyl carrier protein (BCCP). It is organized as a homotetramer. PC catalyzes the conversion of pyruvate to oxaloacetate, and is involved in gluconeogenesis and energy production through replenishment of the tricarboxylic acid (TCA) cycle with oxaloacetate. Adequate energy production via the TCA requires not only a constant supply of acetylCoA but also a fairly constant pool of the catalytic intermediates of the Krebs cycle including oxaloacetate, the key intermediate that condenses with acetylCoA to "initiate" the cycle. As shown in Fig. 1, PC is also closely linked to the urea cycle, because aspartate, the citrulline cosubstrate of argininosuccinate synthetase, is produced from oxaloacetate through transamination.

In striking contrast to genetic defects affecting the mitochondrial respiratory chain (MRC), PC deficiency (OMIM 266150) is very rare [1] as its estimated incidence of 1 in 250 000 births (http://ghr.nlm.nih.gov). PC deficiency is an autosomal recessive disorder with three nosological forms reviewed in 2010 by Marin-Valencia et al. [2]. These forms differ in the severity of clinical and biochemical manifestations: the B or "French" phenotype with neonatal onset and severe outcome, the A form or "North American phenotype"

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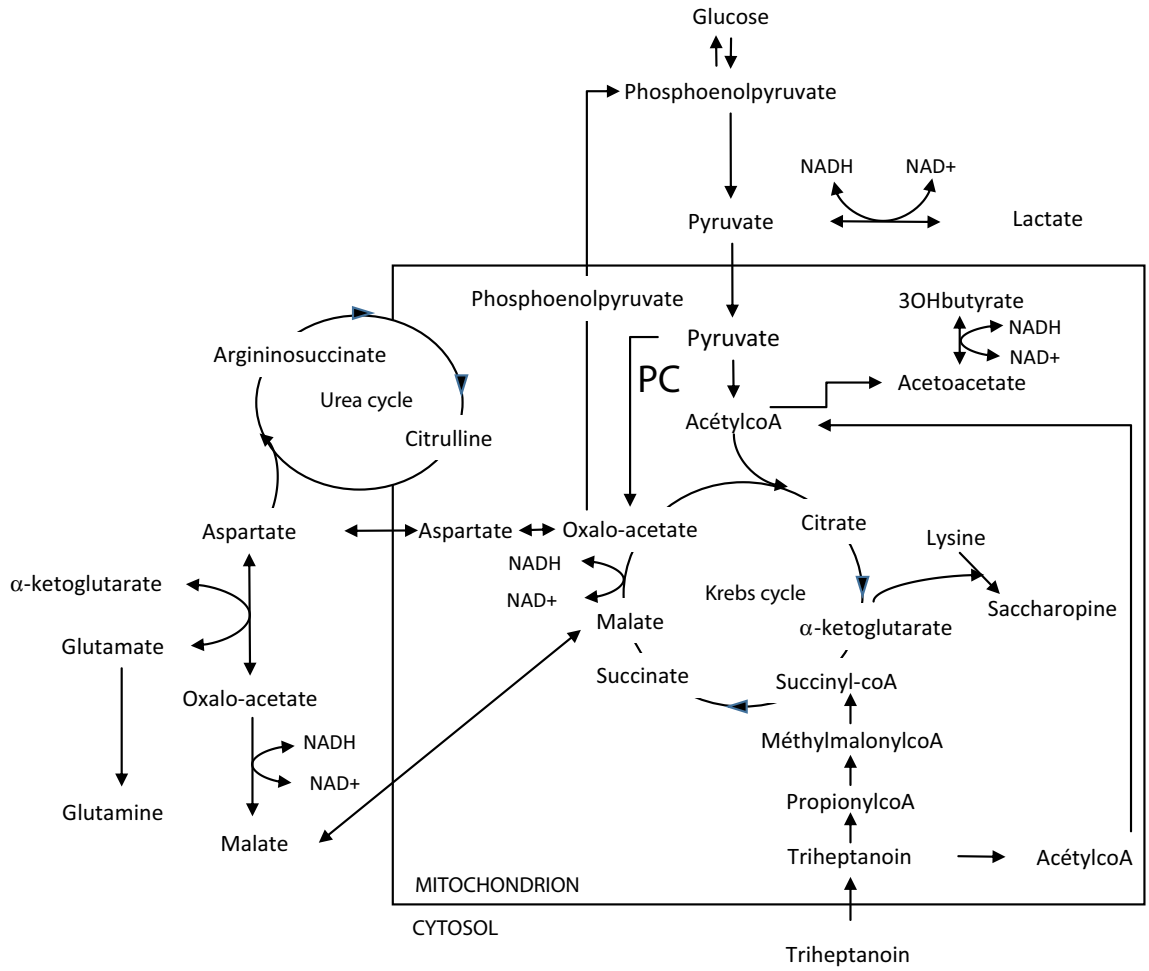

Fig. 1. Functions of pyruvate carboxylase (PC), and its close relation to the urea cycle and the Krebs cycle.
Adapted from [2].

Table 1
Clinical, biochemical and genetic findings at diagnosis in patient 1 and patient 2.

	Patient 1	Patient 2
Age of onset	18 months	Neonatal
Clinical findings	Lactic acidosis following gastro-enteritis	Lactic acidosis
	Developmental delay	Neurological distress
		Hepatic failure
Laboratory investigation	pH = 6.98	pH = 7.15
	Lactate: 11.3 mmol/L	Lactate = 17 mmol/L
	Increased plasma L/P ratio	Increased plasma L/P ratio
	LCR 3-OHB/AcAc ratio in the lower range	Decreased plasma 3-OHB/AcAc ratio
	Ammonemia: 70 μmol/L	Ammonemia: 268 μmol/L
	Plasma amino acids:	Plasma amino acids:
	Alanine: 298 μmol/L	Alanine: 958 μmol/L
	Proline: 114 μmol/L	Proline: 801 μmol/L
	Lysine: 136 μmol/L	Lysine: 713 μmol/L
	Glutamine: 327 μmol/L	Glutamine: 264 μmol/L
	Citrulline: 6 μmol/L	Citrulline: 158 μmol/L
	Urinary organic acids:	Urinary organic acids:
	Lactic acid: 59 mol/mol creatinine	Lactic acid: >75 mol/mol creatinine
	3-OHB: 45 mol/mol creatinine	3-OHB: 8359 mmol/mol creatinine
	Complex IV: 180 nmol/min/mg proteins	Complex IV: 223 nmol/min/mg proteins
Genetics	c. 808C>T; p.Arg270Trp	c. 1023-1G>T (IVS7-1G>T); p.Asp341GlufsX351
	c. 1892G>A; p.Tyr631Gln	c.911A>G; p.Tyr304Cys
Outcome	8 year-old: needs specialized school	Death at 6 months

L: lactate; P: pyruvate; 3-OHB: 3-hydroxybutyrate; AcAc: aceto-acetate; normal range: plasma ammonemia: 15–45 μmol/L; alanine: 174–375 μmol/L; proline: 93–233 μmol/L; lysine: 85–241 μmol/L; glutamine: 423–545 μmol/L; citrulline: 21–38 μmol/L; lactic acid: <76 mmol/mol creatinine; 3-hydroxybutyrate: <99 mmol/mol creatinine; complex IV: 308–457 nmol/min/mg of protein.