The Genetic and Phenotypic Spectrum of Cytosolic Phosphoenolpyruvate Carboxy Kinase Deficiency.

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Introduction

• Cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C), encoded by PCK1 gene (MIM # 614168), is a rate-limiting enzyme in gluconeogenesis.

• It catalyses the decarboxylation of oxaloacetate (OAA) to phosphoenolpyruvate (PEP, Figure 1).

• Biallelic mutations in PCK1 have been reported in patients with hypoglycemia, transient liver dysfunction, and biochemical disturbances suggestive of mitochondrial abnormality and, in some cases, proximal urea cycle defect.

• To date, only nine patients, confirmed by molecular testing, have been reported in the literature. We report on the tenth patient with PEPCK-C deficiency. We also provide review of the phenotypic and genetic spectrum of the patients reported in the literature.

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Figure 1: Schematic representation of the glycolysis/ gluconeogenesis pathway. PC: pyruvate carboxylase, PDHC: pyruvate dehydrogenase complex, PEPCK-C: cytosolic phosphoenolpyruvate kinase, PEPCK-M: mitochondrial phosphoenolpyruvate kinase.
Case Identification

The index is a male born at term

Perinatal history: Uneventful pregnancy & delivery.
Neonatal hypoglycemia (0.5 mmol/L).
Birth parameters: Appropriate for gestational age.
Family history: noncontributory.

Clinical presentation

Year of life 2:
Episodes of hypoglycemia, lethargy, limb, disorientation, hypothermia, and hepatomegaly & splenomegaly during a concurrent illness and fasting for 15 hours.

Initial workup

• Newborn screening: negative.
• Profound hypoglycemia
• Elevated lactate: 6.7 mmol/L.
• Massive ketonuria.
• Metabolic acidosis: HCO3: 16 mEq/L.
• Mildly elevated transaminases.
• Creatinine phosphokinase, uric acid, triglyceride: normal.
• Endocrinology workup: normal.

Case presentation

Subsequent episodes

The index had four subsequent episodes: at 26 months, 3.5 years, 7.5 years and 9 years.
All episodes occurred during prolonged fasting and/or concurrent illnesses.

Management

Acute: Intravenous dextrose 10% infusion during prolonged fasting.
Chronic:
• Fasting avoidance.
• Frequent meals/snacks.
• Carbohydrate and fat rich sick-day formula during concurrent illnesses.
• Bedtime dose of uncooked cornstarch.

Long-term follow up

He is currently 15-years-old.
Age-appropriate growth and development.
No dietary restrictions or prolonged supplement intake.
## Results

Table 1: Summary of the biochemical, radiological and genetic investigations in the index:

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Results</th>
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<tbody>
<tr>
<td>Plasma amino acids (µmol/L)</td>
<td>Unremarkable throughout all episodes of decompensation.</td>
</tr>
<tr>
<td>Acylcarnitine profile (µmol/L)</td>
<td>Unremarkable throughout all episodes of decompensation.</td>
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| Urine organic acids (mmol/mol creatinine).  | **Day of life 2:**  
Massive:  
Lactic aciduria.  
Ketonuria.  
2-ketoglutaric aciduria  
Mild:  
Citric acid cycle metabolites including: fumaric and aconitic acidurias.  
Dicarboxylic aciduria.  
Glutaric aciduria.  
2-keto-3-methylvaleric aciduria.  
**Subsequent decompensation:**  
Moderate elevation in 2 ketoglutaric acid.  
Mild increase in fumaric acid.  
**Between decompensation episodes:**  
Unremarkable profile. |
| Abdominal ultrasound                        | **At 6 months:** moderate diffuse hepatomegaly with diffuse coarse echotexture; in addition to mild splenomegaly.  
Repeat at 3 years: hepatosplenomegaly fully resolved. |
| Molecular testing                           | sequencing of *AGL, G6PC, PYGL, SLC37A4, GYS2, PHKA2, PHKG2*: negative.                                                                    |

Hypoglycemia gene panel: compound heterozygous for two variants in *PCK1*:  
- Previously reported, maternally inherited, pathogenic c.925G>A (p.Gly309Arg)  
- Novel, paternally inherited, likely pathogenic c.824del (p.Gly275Valfs*21).
Discussion

• PEPCK-C deficiency presents with variable degrees of infantile or early childhood hypoglycemia, ketonuria, elevated lactate, metabolic acidosis, transient liver dysfunction and hepatomegaly, thus mimicking glycogen storage diseases (GSD). Occasionally patients may present with hyperammonemia, thus mimicking urea cycle defects or organic acidurias.

• The earliest sign of PEPCK-C deficiency is neonatal hypoglycemia, which is usually attributed to other neonatal disorders.

• The presentation is usually triggered by prolonged fasting (overnight, decreased oral intake due to vomiting) and/or concurrent illness. However, some patients may exhibit hypoglycemia in the absence of precipitating factor.

• Patients with PEPCK-C deficiency exhibit high urinary excretion of citric acid cycle metabolites, mainly fumaric acid and 2-ketogluatric acid during episodes of metabolic decompensation. However, they have normal profiles outside these episodes. Plasma amino acids and acylcarnitine profile are helpful in excluding other disorders.

• To date, there are seven reported causative variants, most of which are located in exons 2 and 6 (Figure 2). However, data from literature does not indicate a mutation hot-spot.

• PEPCK-C deficiency is a treatable disorder, and the prognosis is favourable. However, severe cases with hypoglycemic encephalopathy and seizures leading to death have been reported. Thus, early diagnosis, using a combination of biochemical and molecular testing, is crucial.

• Treatment is achieved by intravenous dextrose 10% infusion during episodes of prolonged fasting, avoidance of fasting by providing frequent meals and/or snacks, high carbohydrate sick-day formula during concurrent illnesses, and a bedtime dose of uncooked cornstarch.

Figure 2: schematic representation of the disease causing variants reported in PEPCK-C deficiency.
Conclusion
The reported phenotypic spectrum of the ultra-rare PEPCK-C deficiency ranges between severe neonatal hypoglycemia, encephalopathy and brain edema leading to death, and a milder phenotype with fasting hypoglycemia and transient liver dysfunction presenting later in life. Thus, early diagnosis, using combination of biochemical and genetic investigations, is recommended. The long-term follow up is suggested to be favourable.

Acknowledgement
We would like to thank the patients and their family for their contribution in this case report. Our appreciation is also extended to all clinical and laboratory medical staff in both our centre and in the involved diagnostic laboratories for their participation.

References