From floppy infant to pyruvate dehydrogenase complex (PDHC) deficiency – a diagnostic challenge
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Title figure:
pyruvate dehydrogenase complex from www.pnas.org
Generalized muscular hypotonia is a diagnostically challenging presentation in the term neonate («floppy infant»). Differential diagnosis includes myopathies, chromosomal disorders and specific monogenetic syndromes, endocrinopathies, inborn errors of metabolism, and other acute (e.g. neonatal sepsis) or chronic conditions (1, 2). In 85–90% of cases, a central disorder is causative, while in 7–9% a peripheral disorder can be identified. 8–13% of cases remain unsolved. Infants presenting with generalized hypotonia and symptoms such as lethargy, poor facial gestures, seizures, irregular breathing patterns are more likely to suffer from central disorders. In contrast, muscular weakness in the presence of normal alertness and cognitive development suggests peripheral disorders. The most common clinical condition – though a diagnosis of exclusion – is benign congenital hypotonia (1, 2).
This boy was spontaneously delivered at 40 2/7 weeks of gestation to a healthy 29-year-old mother after an uneventful pregnancy. Family history was non informative with a healthy three-year-old sister and a father with malignant hyperthermia. Neonatal transition, as well as physiological stability over the first 24 hours of life were considered normal. During the second day of life, the infant’s condition deteriorated and he developed progressive feeding difficulties, generalized muscular hypotonia, and tachydyspnea leading to admission to the neonatal intensive care unit.

On admission, body weight was 2650 g (<P3), length was 49 cm (P11); head circumference was 33 cm (P5). Minor dysmorphic features were noted such as a small anterior fontanel, overlapping sutures and rudimentary auricular helices. Initial laboratory work-up revealed a compensated metabolic acidosis (pH 7.32, pCO₂ 2.2 kPa, base excess -15.8 mmol/l) with an anion gap of 21.6 mmol/l and an elevated blood lactate of 9.9 mmol/l. Sepsis work-up was normal. On cranial ultrasound, the corpus callosum and gyrus cinguli could not be identified, and external CSF spaces appeared enlarged.

Antibiotic therapy was initiated due to suspected neonatal sepsis. Acidosis was treated with sodium bicarbonate. However, lactate remained elevated (between 10 – 12 mmol/l, normal lactate/pyruvate ratio of 15). Due to the complex clinical picture, continuously elevated lactate, discrete dysmorphic features, cor-
pus callosum agenesis, and deteriorating condition, an extensive metabolic and endocrinological work-up was initiated.

Baseline endocrine assessment, blood glucose, creatine kinase, ASAT and ALAT were normal. Pre- and postprandial lactate measurements were not informative, and carbohydrate loading was not performed. Acylcarnitine profile, organic acids, plasma ammonia were normal, and ketonuria and orotic aciduria were not present thus excluding fatty acid oxidation disorders, aminoacidopathies, organic acidurias, and urea cycle disorders (3, 4). Persistently elevated lactate concentrations together with massively elevated alanine levels (2223 µmol/l; normal 222 – 379 µmol/l) were highly suggestive of a mitochondrial disorder (5). Normal lactate/pyruvate ratio was especially compatible with an energy production disorder at the level of the pyruvate dehydrogenase complex (PDHC) (3, 5).

Based on this hypothesis, thiamine supplementation (80 mg/kg/day) and a ketogenic diet (70/30) were initiated within the first weeks of life. Consequently, serum lactate, pyruvate and alanine concentrations decreased (Fig. 1). Nevertheless, on day 6 of life, the boy developed generalized tonic-clonic seizures. Seizure control was achieved with standard phenobarbitone treatment. Electroencephalography repeatedly demonstrated an abnormal background pattern and increased susceptibility to seizures.
Lactate concentrations over time (A: initial presentation; B: thiamin supplementation and ketogenic diet; fatal deterioration during febrile illness)
Finally, PDHC deficiency was enzymatically confirmed in cultivated skin fibroblasts using the PDH kit and dipstick reader from Mitoscience. Enzyme activity is indicated as mAbs/mU citrate synthase which normalizes the activity to the mitochondrial content. Citrate synthase was measured spectrophotometrically using a coupled assay measuring the conversion of DTNB (2-nitrobenzoic acid) to 5-thio-2-nitrobenzoic acid (TNB). This yellow product (TNB) is observed spectrophotometrically by measuring absorbance at 412 nm (6). Molecular genetic testing revealed a pathogenic mutation (c.986T>G, p.Leu329Arg, in hemizygous form) in the PDHA1-gene and confirmed the X-linked form of PDHC deficiency (subunit E1-alpha). The mutation was not found in the mother and therefore most likely had occurred de novo in the child. Maternal germline mosaicism cannot be excluded and recurrence risk therefore is estimated at about 1%.

After discharge, compliance with the ketogenic diet remained well, blood ketone bodies were within target range (2.2 – 3.9 mmol/l), lactate and blood gas analysis normalized, and the child was in a stable metabolic condition. Even though phenobarbitone could be tapered during the course without recurrence of seizures, and despite developmental support, occupational and physical therapy, the overall clinical course was unfavourable as the boy remained severely floppy with no significant neurodevelopmental progress, and developed progressive microcephaly. In addition, signi-
Significant hearing impairment and visual impairment with nystagmus and absence of fixation were diagnosed.

At the age of nine months, the child was admitted to the hospital due to rapid clinical deterioration during a febrile infection. Immediate cardiopulmonary resuscitation and intensive care was necessary due to acute respiratory insufficiency and apnoea shortly after admission. Subsequently, the child presented with very severe metabolic acidosis (pH 6.9, BE -27 mmol/l, lactate concentration 16 mmol/l) (Fig. 1). MRI of the brain revealed brain atrophy, aplasia of the corpus callosum, as well as hyperintensity of the basal ganglia (Fig. 2).

After thorough evaluation of the extremely poor prognosis and following discussions with the family and the institutional ethical board, care was redirected towards palliation. The boy died within two hours after extubation.
MRI of the head at the age of 9 months (T2-weighted images): cerebral atrophy, aplasia of corpus callosum and hyperintense basal ganglia.

Fig. 2
Neonatal lactic acidosis may occur in a wide range of conditions, the most common being perinatal asphyxia in the neonate. Other frequent reasons for lactic acidosis are sepsis, shock, cardiac failure or cardiomyopathy, hypotension, renal failure, cerebral hemorrhage and inborn metabolic disorders (3, 4, 7).

Even though the most frequent problems in an acutely deteriorating neonate are sepsis or asphyxia, other differential diagnoses must be considered. Since inborn errors of metabolism are triggered by catabolism (physiologically present in the early postnatal period) and exacerbated by infections, the differential diagnosis of sepsis in a newborn should include inborn errors of metabolism. This is particularly important as treatments for an increasing number of inborn errors have become available. A straightforward clinical approach to diagnosis in a term neonate presenting with floppiness includes:

- History suggestive for pregnancy complications, birth trauma, asphyxia?
- Family history and pedigree including information on consanguinity
- Chronological sequence: is it a primary «floppy infant» or has the symptom developed over time?
- Are other organs affected? Are signs of encephalopathy present?
- Is the overall condition stable, improving or deteriorating?
The metabolic work-up should include the following investigations: blood chemistry and blood cell count, plasma ammonia, lactate, blood glucose, blood gas analysis with anion gap, amino acids, carnitine, acyl-carnitine profile, homocysteine and amino acid profile should be performed and completed by analysis of ketones, organic acids and eventually orotic acid in urine. In addition, lumbar puncture must be considered. Ketonuria is always pathological in a newborn and an elevated anion gap suggests a pathological accumulation of organic acids.

In the presented case, an uneventful history, dysmorphic features, rapidly deteriorating condition, seizures, encephalopathy, associated with persistent lactic acidemia were highly suggestive of a metabolic disorder.

The PDHC is a key player in energy metabolism. It connects glycolysis and the citric acid cycle by allowing the oxidative decarboxylation of pyruvate to acetyl-CoA (Fig. 3). PDHC deficiency is a rare disorder with an incidence between 0.06‰ (8) and 0.09‰ (9). Since most mutations are sporadic, the recurrence rate is very low (10, 11). Severe PDHC deficiency results in a shift towards increased lactate and alanine synthesis from pyruvate to the detriment of ATP production (5).

Severe deficiencies (<15% residual activity), such as seen in our patient, are associated with congenital malformations of the brain (e.g. hypoplasia of the
Diagram of a simplified version of the citric acid cycle. The dashed line indicates the blocked pathway in PDHC deficiency; because pyruvate does not proceed to acetyl-coenzyme A, it is shunted to other pathways that produce lactate and alanine (adapted from Medscape Reference, November 2009)
corpus callosum or migration disorder) and prognosis is very poor with many patients not surviving infancy or early childhood (10). At present, treatment consists of a ketogenic diet and thiamine supplementation. Ketogenic diet is beneficial in PDHC deficiency because it provides an alternative source of energy (12). However, despite the biochemical response (lower pyruvate and lactate concentrations), neurological and overall outcomes remain unaltered (13). Given the severity of the disorder, ethical considerations are vital once diagnosis has been established.

Patients with milder forms of PDHC deficiency (i.e. with higher residual PDHC activity) show a broad and faceted clinical picture. They can present with Leigh’s encephalopathy, intermittent ataxia, dystonia, as well as psychomotor and neurodevelopmental delay of variable degrees.


