Propionic Acidaemia

Synonyms: propionyl-CoA carboxylase deficiency, ketotic hyperglycinaemia

This is a rare metabolic disorder which can present with vomiting, dehydration and encephalopathy but also with developmental delay and haematological disorders.[1]

- The condition predisposes to stroke, specifically bilateral infarcts of the basal ganglia involving caudate, putamen and globus pallidus.
- Milder forms of the condition exist.
- It may be underdiagnosed.
- Propionyl-CoA is an important intermediate in the metabolism of several amino acids and is also produced by oxidation of odd-numbered fatty acids.[2] Patients are intolerant to protein.

Pathophysiology

- This is a genetic defect of metabolism, inherited as an autosomal recessive.
- The enzyme propionyl co-enzyme A (CoA) carboxylase is deficient.
- Severe ketoacidosis is precipitated by ingestion of protein.
- A defect has been described at gene map locus 3q21-q22 but another variation with a defect on chromosome 13 has been described and there may be a few variations of the condition.[1,2] Online Mendelian Inheritance in Man (OMIM) lists eight.[2]
- The problem lies in the metabolism of the amino acids isoleucine, valine, threonine and methionine. They are essential amino acids and so management is based on keeping their dietary content low rather than total exclusion.[3]

Epidemiology[4]

- It is a rare condition that on a worldwide basis probably affects about 1 child in 100,000 births.
- Mild forms of the disease are probably more common and the true incidence may be as high as 1 case in 18,000 of the population.
- In certain areas like Saudi Arabia, the incidence may be as high as 1 in 2,000 to 5,000 births.
- It is difficult to assess how much is due to spontaneous mutation.
- Many cases may not be diagnosed and so the incidence may be rather higher than suspected.
- Consanguineous marriage is a common risk factor.[5]

Presentation[6]

The fetus is protected in utero by the mother’s circulation and metabolism and so presentation is often in infancy. This will depend upon the degree of deficiency of the enzyme. Some have divided patients into two subgroups:

- Early-onset:
  - Present within the first week of life.
  - General learning disability.
  - Early death.

- Late-onset:
  - Present after 6 weeks of age and can (in mild forms of the disease) present much later in life.
  - Characterised by severe movement disorders and dystonias.
More specifically:

- Presentation can be with severe ketoacidosis and pH as low as 6.8. There is shock, hypoxia and there may be serious brain damage. Death can result.
- A more usual presentation is failure to thrive with feeding intolerance.
- Excessive levels of ammonia produce a repeated insult to the brain that causes general learning disability. Somnolence is common.
- An attack is followed by pancytopenia that predisposes to overwhelming and possibly fatal infection. The presence of infection to account for illness makes it easy to overlook the metabolic defect.
- Usually there is no family history but sometimes an older infant or young child may have a long history of episodic lethargy, anorexia, vomiting and acidosis that responds to short hospital stays with intravenous glucose and bicarbonate administration.
- Cardiomyopathy can be rapid and fatal.
- Psychosis has been reported as a late presentation.\[7\]

**Differential diagnosis**

A wide variety of conditions may form part of this list, depending on the presentation.\[3, 8\]

- Aseptic meningitis.
- Haemophilus meningitis.
- Stroke:
  - Basilar artery thrombosis.
  - Posterior cerebral artery stroke.

- Metabolic disorders:
  - Disorders of carbohydrate metabolism.
  - Anderson-Fabry disease.
  - Homocystinuria.
  - Note that, of 100 inborn errors of metabolism, only about 20 are amenable to treatment.\[9\]

- Infective endocarditis (neurological complications).
- Tuberous sclerosis.
- Haematological disorders:
  - Sickle cell disease.
  - Thrombocytopenia.

**Investigation**\[3\]

The following findings help to confirm the diagnosis:

- Urine will show ketones. This is unusual in infants and should raise suspicion.
- There is metabolic acidosis with serum electrolytes showing a raised anion gap (normal range 10-18 mmol/L).
- Blood ammonia is elevated. This indicates the cause for disturbance of mental status.
- Plasma lactate is often raised but not enough to account for the anion gap. This should also raise suspicion.
- Urinary organic acids confirm the diagnosis. Large increases in beta-hydroxy propionic acid, lactic acid and methylcitrate excretion are found.
- The ultimate test is leukocyte propionyl-CoA carboxylase activity. It gives definitive biochemical diagnosis and allows genetic counselling.
- If the diagnosis is not made in life it is unlikely to be made post-mortem.

However, it is likely that the full work-up of patients presenting with typical (but nonspecific) signs and symptoms will include a wider range of tests in keeping with the differential diagnoses outlined. Inborn errors of metabolism present in a variety of ways (five main presentations have been observed) and faced with an infant’s deteriorating condition, emergency treatment and investigations have to be pursued.\[10\] These will include, for example:

- FBC (often reveals neutropenia and thrombocytopenia), electrolytes and blood gases.
- Blood glucose (to exclude other causes of acidosis).
- LFTs (to exclude acidosis from liver disease).
- Full range of imaging investigations (appropriate for a young patient with stroke).

**Management**\[3\]

The severe metabolic ketoacidosis in this disorder requires vigorous alkali therapy and protein restriction. Ammonia, acid-base balance and anion gap are important biochemical indicators to identify metabolic decompensation and to assess severity.\[11\] Oral antibiotic therapy to reduce gut propionate production may also prove useful.\[1\]

- Usually the child is severely unwell on presentation and the clinical imperative is the correction of the ketoacidosis, dehydration and electrolyte imbalance. Fluid, electrolytes and bicarbonate are required. Sometimes glucose and insulin are required.
A temporary cessation of intake of protein is required, after which the offending amino acids should be permitted in very
limited amounts. A protein intake below 1.5 grams per kilogram body weight per day is often required.

If breast-feeding occurs it must be monitored carefully. Diet should be individualised with the aim of restricting propiogenic substrates (valine, methionine, isoleucine, threonine and odd chain fatty acids), while encouraging normal protein synthesis and preventing protein catabolism, amino acid deficiencies and growth restriction.

L-carnitine supplementation at a dose of 50-100 mg/kg/day should be given.

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Anti-epileptic medication and therapy of arrhythmias may be needed.

Orthoptic liver transplantation (replacement of all or part of the liver with a donor liver in the same anatomical position) is indicated in patients with frequent metabolic decompensations, uncontrollable hyperammonaemia and restricted growth. Pre-operatively it is important to minimise the severity of metabolic acidosis by maintaining optimal tissue perfusion, avoiding hypotension, preventing hypoglycaemia and providing bicarbonate.

Continuous haemofiltration, extracorporeal membrane oxygenation (ECMO) and left ventricular assist devices have been used while awaiting liver transplant.

Prognosis

Strict adherence to the diet is required.

Brain damage is common and life expectancy limited.

Heart failure and cardiomyopathy are commonly reported causes of mortality.

The degree of deficiency of the enzyme has great prognostic significance.

Prevention

After genetic counselling it is possible to offer prenatal testing with a view to termination of pregnancy (TOP) as the prognosis is so very poor. If two carriers have been identified (eg when investigating the cause of death of a previous offspring) it may be possible to perform preimplantation genetic diagnosis (PGD). In this technique, embryos conceived by in vitro fertilisation are tested and only those which are healthy are implanted into the uterus.

Prenatal testing can be performed:

- Amniocentesis: propionic acidemia can be diagnosed either by an elevated quantity of the metabolite methylcitrate in amniotic fluid or by deficient activity of propionyl-CoA carboxylase in amniocytes.

- Chorionic villous sampling: prenatal diagnosis of an affected fetus, based on DNA analysis in chorionic villus tissue, can also be performed.

Screening has been suggested but it is a rare condition that can be missed by the test and it is doubtful whether this improves quality of life or gives value for money.
Further reading & references


1. Proponic Acidemia; Online Mendelian Inheritance in Man (OMIM)
2. Propionyl-CoA Carboxylase, Beta Subunit; PCCB; Online Mendelian Inheritance in Man (OMIM)

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