Pyruvate Dehydrogenase Complex Deficiency (PDCD)

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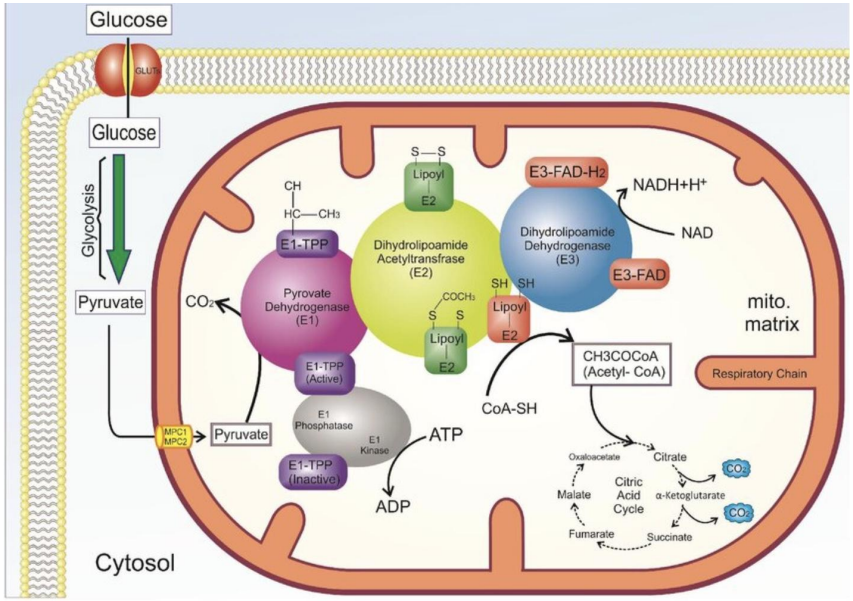
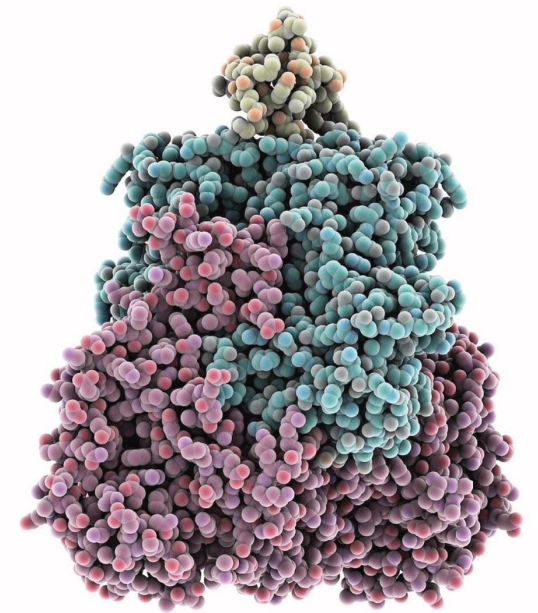
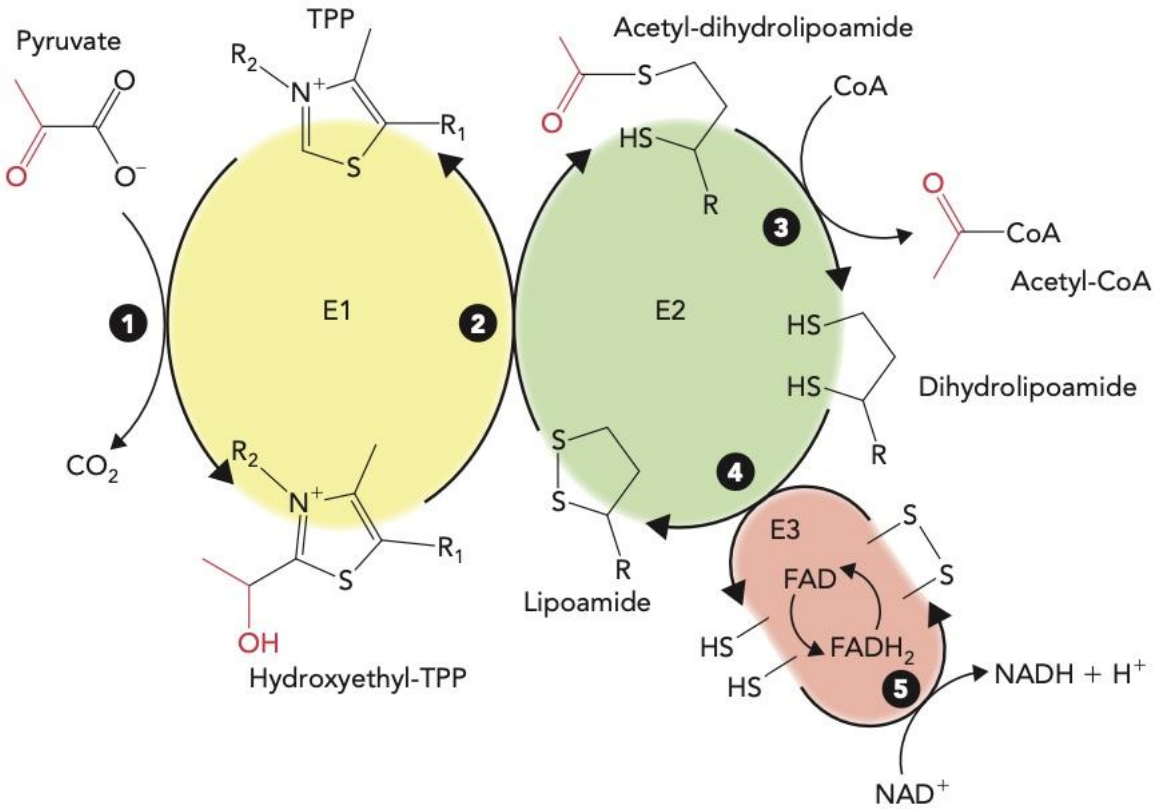


Pyruvate Dehydrogenase (1)

PDH is part of a multi-enzyme complex composed of three main components:

1. E1: Pyruvate Dehydrogenase
    - Does the decarboxylation of pyruvate (removes CO_2).
2. E2: Dihydrolipoyl acetyltransferase
    - Transfers the resulting acetyl group to CoA.
3. E3: Dihydrolipoyl Dehydrogenase
    - Regenerates the oxidized form of the coenzymes used.





1. The E1 subunit (pyruvate dehydrogenase) binds pyruvate and catalyzes a decarboxylation reaction, resulting in the formation of hydroxyethyl-TPP and the subsequent release of CO2. (2)

2. The hydroxyethyl-TPP moiety of E1 reacts with the disulfide of the lipoamide group on the N-terminal domain of the E2 subunit (dihydrolipoyl acetyltransferase). This generates acetyl-dihydrolipoamide through a thioester bond. (2)

3. The E2 acetyl-dihydrolipoamide group carries the acetyl group from the E1 catalytic site across a gap in the complex to the E2 catalytic site, where it reacts with CoA to yield acetyl-CoA and fully reduced dihydrolipoamide. (2)

4. The dihydrolipoamide group then swings over to the E3 subunit (dihydrolipoyl dehydrogenase), where it is reoxidized to the disulfide by a transfer of 2 e– and 2 H+ to a disulfide contained on the E3 subunit, forming a reduced dithiol. The reduced dithiol on the E3 subunit is reoxidized by transferring 2 e– and (2)

2 H+ to the E3-linked FAD moiety, transiently forming E3-FADH2.

5. The E3-FADH2 coenzyme intermediate is reoxidized in a coupled redox reaction that transfers 2 e– to NAD+, producing NADH + H+ (2)

$$\text{Pyruvate} + \text{CoA} + \text{NAD}^+ \rightleftharpoons \text{Acetyl-CoA} + \text{CO}_2 + \text{NADH} + \text{H}^+$$

$$\Delta G^{\circ\prime} = -33.4\ \text{kJ/mol}$$

Cofactors Required (3)

The PDH complex needs 5 cofactors to function properly:

1. Thiamine pyrophosphate (TPP) – Vitamin B1
2. Lipoic acid
3. Coenzyme A (CoA) – from Vitamin B5
4. FAD (Flavin adenine dinucleotide) – from Vitamin B2
5. NAD^+ (Nicotinamide adenine dinucleotide) – from Vitamin B3

Cofactor	Other Name	Daily Requirement	Top Food Sources
Vitamin B1	Thiamine	♂ 1.2 mg / ♀ 1.1 mg	Whole grains, pork, legumes, sunflower seeds
Lipoic Acid	— (not a vitamin)	No official RDA *(body synthesizes small amounts)*	Spinach, broccoli, potatoes, organ meats (liver, heart)
Vitamin B2	Riboflavin	♂ 1.3 mg / ♀ 1.1 mg	Eggs, dairy, lean meats, green veggies, fortified cereals
Vitamin B5	Pantothenic Acid	5 mg	Chicken, beef, eggs, mushrooms, avocados, whole grains
Vitamin B7	Biotin	30 mcg	Egg yolks, nuts, seeds, salmon, sweet potatoes

Complex

The conversion of pyruvate to acetyl-CoA by the pyruvate dehydrogenase complex is the necessary transition from glycolysis to the citrate cycle.

The pyruvate dehydrogenase reaction is essentially irreversible and plays a central role in metabolism by controlling the amount of carbohydrate that is converted to ATP or stored as fatty acids in adipose tissue.

The reaction is an oxidative decarboxylation.

Without PDH, the cell can't effectively use glucose for energy under aerobic conditions.

Cells switch to anaerobic glycolysis, producing less ATP and more lactic acid, leading to lactic acidosis.

PDCD

Pyruvate Dehydrogenase Complex Deficiency (PDCD) is a rare, inherited metabolic disorder that affects the body's ability to convert carbohydrates into usable energy. It's most commonly seen in infants and young children and can lead to a range of neurological and muscular problems. (1)

PDCD is caused by a malfunction in the pyruvate dehydrogenase complex (PDC), a group of enzymes found in the mitochondria. This complex is crucial for converting pyruvate (the end product of glycolysis) into acetyl-CoA, which enters the citric acid cycle (Krebs cycle) to produce ATP (energy). (1)

There are 6 genes that are associated with PDCD (4):

- PDHA1, PDHB, PDHX, DLAT, DLD, and PDP1.
- PDHA1 is the most common of these and accounts for 90%

  of PDCD cases (1), and affects the E1 subunit (2)

PDHA1 is located on the X chromosome, so (4):

- Males (XY) are more severely affected
- Females (XX) may be carriers or show mild to moderate

  Symptoms depending on X-inactivation.

Gene	What it Encodes	Function in PDC
PDHA1	E1 alpha subunit	⚙️ Catalyzes the first step of the PDC reaction
PDHB	E1 beta subunit	Works with E1α to decarboxylate pyruvate
PDHX	E3-binding protein	Links E1 and E3 components together
DLAT	E2 subunit	Transfers the acetyl group to CoA
DLD	E3 subunit	Regenerates oxidized lipoamide (helps complete the cycle)
PDP1	Pyruvate dehydrogenase phosphatase	Regulates PDC by reactivating it

PDH Summary

Normal Pathway:

1. Glucose → Glycolysis → Pyruvate
2. Pyruvate is transported into the mitochondria.
3. The pyruvate dehydrogenase complex (PDC) converts pyruvate → acetyl-CoA.
4. Acetyl-CoA enters the Krebs cycle → leads to ATP production via oxidative phosphorylation.

In PDCD:

- The PDC is partially or completely non-functional.
- Most often due to mutations in the PDHA1 gene, which encodes the E1-alpha subunit of the PDC.
- Result: Pyruvate cannot be efficiently converted into acetyl-CoA.
- Pyruvate builds up and is shunted to form lactate and alanine → lactic acidosis and alaninemia.

Symptoms (5)

- Developmental delay
- Hypotonia (low muscle tone)
- Seizures
- Lactic acidosis (especially during illness or fasting)
- Ataxia, poor feeding, and failure to thrive

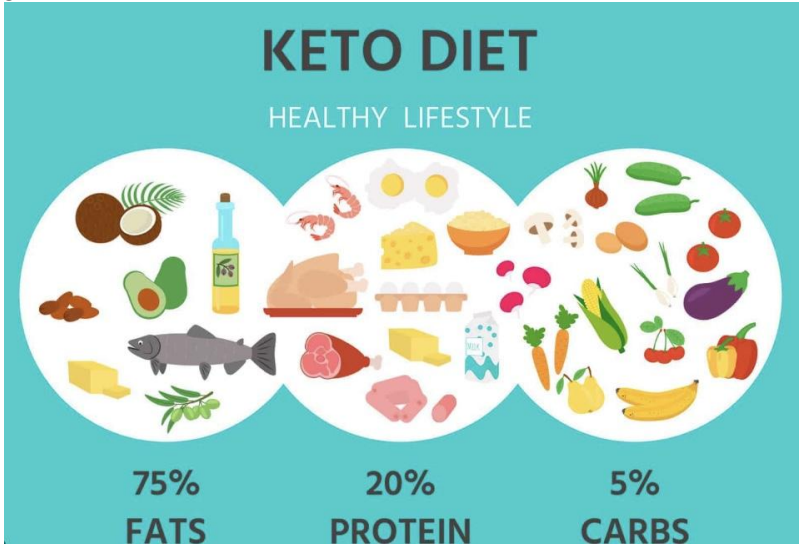
Diagnosis (5)

- Elevated lactate and pyruvate in blood and CSF
- Low lactate-to-pyruvate ratio
- Enzyme activity assays
- Genetic testing (e.g., PDHA1 mutations)

Treatment (5)

No cure, but management may include:

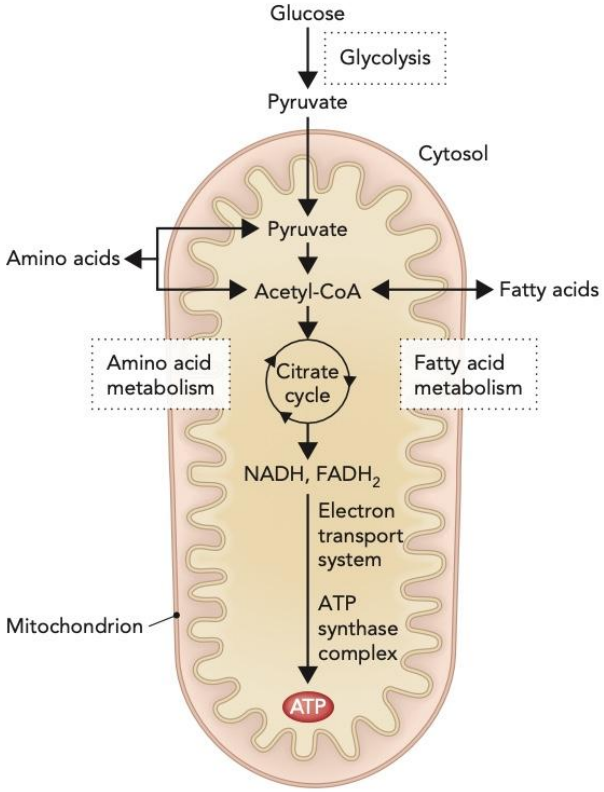
- Ketogenic diet (high-fat, low-carb) to bypass glycolysis and provide alternative energy.
- Thiamine (Vitamin B1) supplementation – a cofactor of PDC – sometimes helps enhance residual enzyme activity.
- Supportive care: seizure control, physical therapy, treatment of acidosis.



Krebs Cycle and Oxidative Phosphorylation (2)

Due to this deficiency,

- Fewer electrons enter the ETC because the Krebs cycle is disrupted.
- This means less NADH/$FADH_2$, less oxidative phosphorylation, and less ATP.
- Cells, especially in the brain and muscles, become energy-starved.



Anaerobic Respiration and Lactic Acidosis (6)

Even if oxygen is available, cells act like they are in anaerobic conditions

Because aerobic ATP production is impaired:

- Cells shift to anaerobic glycolysis for energy
- Pyruvate → Lactate (via lactate dehydrogenase)
- This produces a little ATP, but much less than aerobic metabolism

Lactate builds up in the blood and tissues

- Leads to acidosis
- Leads to a vast range of complications

Disorders associated with PDCD Deficiency (5)

- Ventriculomegaly
- Corpus Callosum Dysgenesis
- Lactic acidosis
- Leigh Syndrome

Ventriculomegaly (7)

- Stems from energy deficiency in the brain
- The brain is extremely energy-dependent, especially during development
- In PDCD, impaired oxidative phosphorylation causes chronic ATP shortage, leading to poor tissue growth and neurodegeneration or atrophy.
- Ventriculomegaly is the enlargement of the brain’s ventricles (fluid-filled spaces).
- Occurs secondarily due to loss of surrounding brain tissue (cerebral atrophy).
- Neurons cannot maintain structure/function without enough ATP
- Over time, brain tissue may shrink or not develop fully
- The ventricles expand to fill the space

Complications (7)

Complications include macrocephaly (enlarged head due to enlarged ventricles).

Bulging fontanelle (soft spot on the baby’s head may appear full or tense)

Developmental delays (motor skills, speech and language, cognitive abilities)

Poor muscle tone

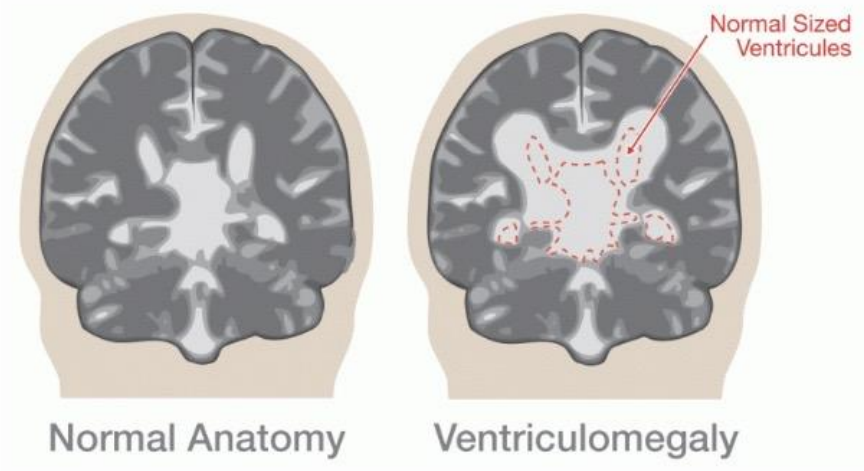
Irritability or Lethargy

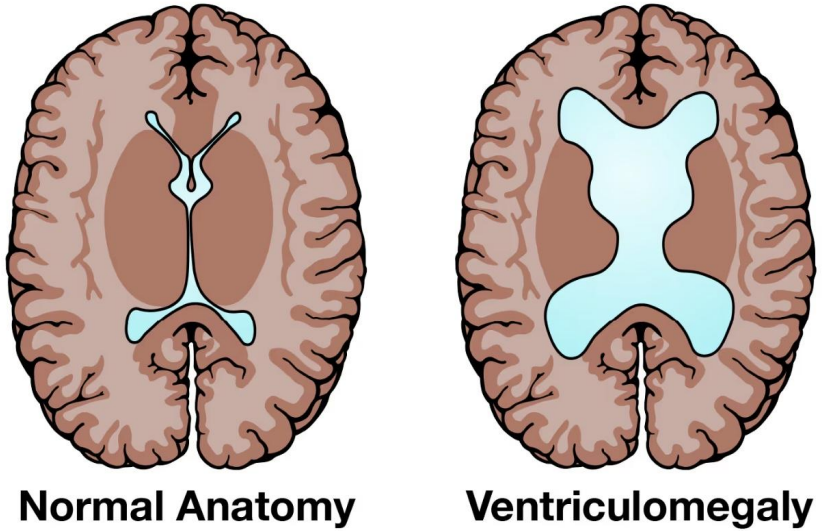
Seizures

Balance and coordination issues

Vision or eye movement problems

Photos (7)


Normal Sized
Ventricules
Normal Anatomy
Ventriculomegaly


Normal Anatomy
Ventriculomegaly

Corpus Callosum Dysgenesis (8)

The corpus callosum is a thick bundle of nerve fibers connecting the two brain hemispheres and begins to form between 12-16 weeks of gestation.

Energy Deficiency in the developing brain interferes with neuronal migration, axon guidance, and white matter formation.

This leads to partial or complete absence (agenesis) or malformation (dysgenesis) of the corpus callosum.

Complications (8)

Developmental delays

Intellectual disability

Seizures

Hypotonia

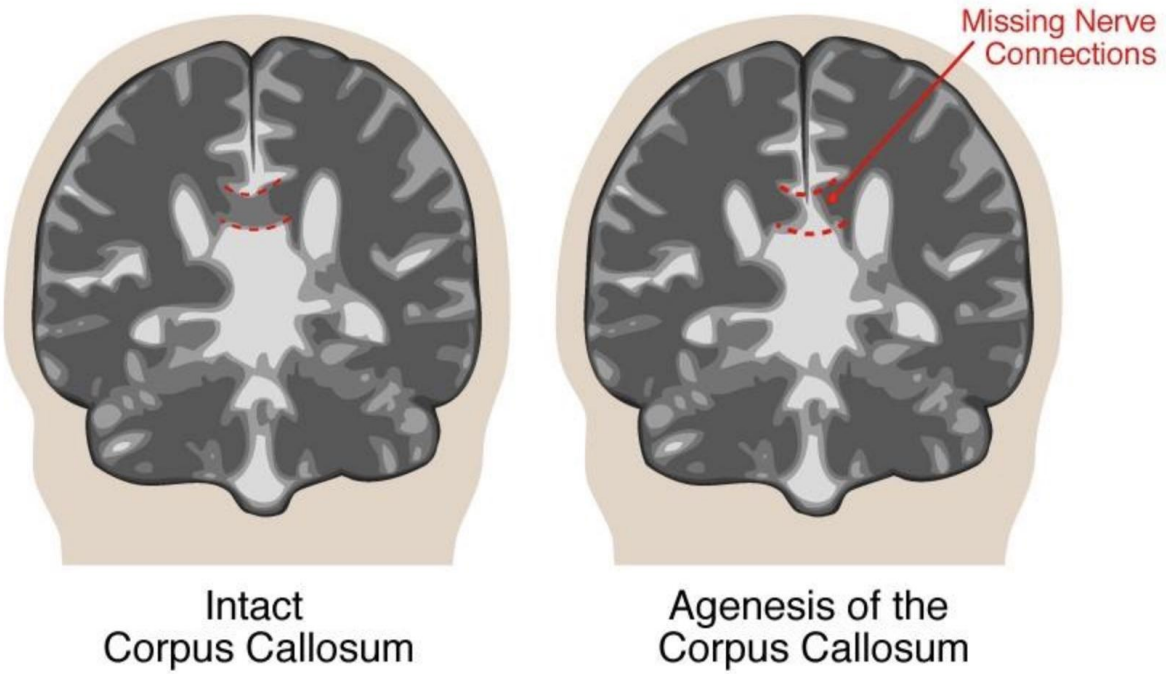
Ataxia

Difficulty with complex problem solving

Social and communication challenges

Visual or sensory processing issues

Photos (8)


Missing Nerve
Connections
Intact
Corpus Callosum
Agenesis of the
Corpus Callosum

Lactic acidosis (6)

In PDCD, the Pyruvate Dehydrogenase Complex is deficient or dysfunctional.

This prevents pyruvate (from glycolysis) from being converted into acetyl-CoA, which is needed to enter the krebs cycle.

With nowhere to go, pyruvate is redirected into other pathways:

- Pyruvate → Lactate via lactate dehydrogenase
- Results in excess lactate

When lactate levels becomes too high, it acidifies the blood.

This leads to lactic acidosis, defined by:

- High lactate concentration
- Low blood pH
- Low bicarbonate

Complications (6)

Rapid breathing

Nausea, vomiting

Lethargy or fatigue

Muscle weakness

Confusion or altered consciousness

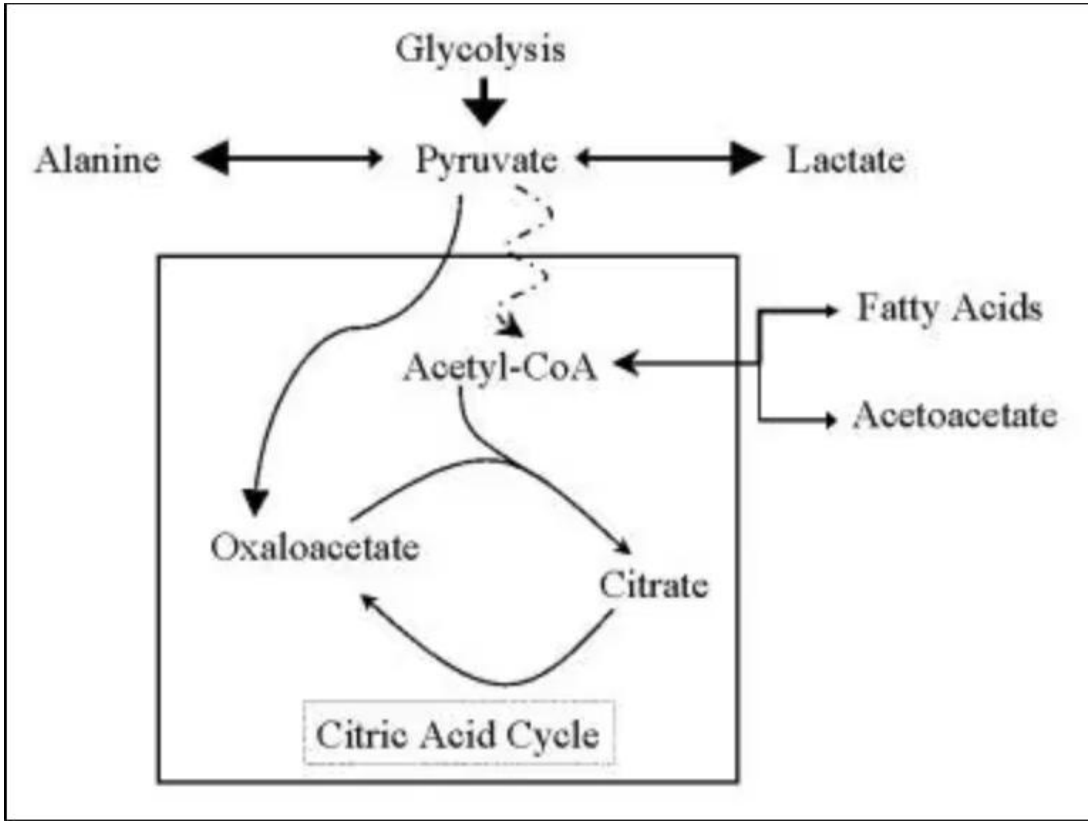
Brain damage

Poor growth and feeding difficulties

Worsening of neurological symptoms

Multi-organ stress

Photos (6)


Glycolysis
Alanine
Pyruvate
Lactate
Fatty Acids
Acetyl-CoA
Acetoacetate
Oxaloacetate
Citrate
Citric Acid Cycle

Leigh Syndrome (9)

Leigh Syndrome is a subacute necrotizing encephalomyelopathy, which causes localized brain lesions in the: Basal ganglia, Thalamus, and Brainstem.

Results from energy failure in PDCD, especially in infants and young children

Complications (9)

Developmental regression

Hypotonia

Ataxia

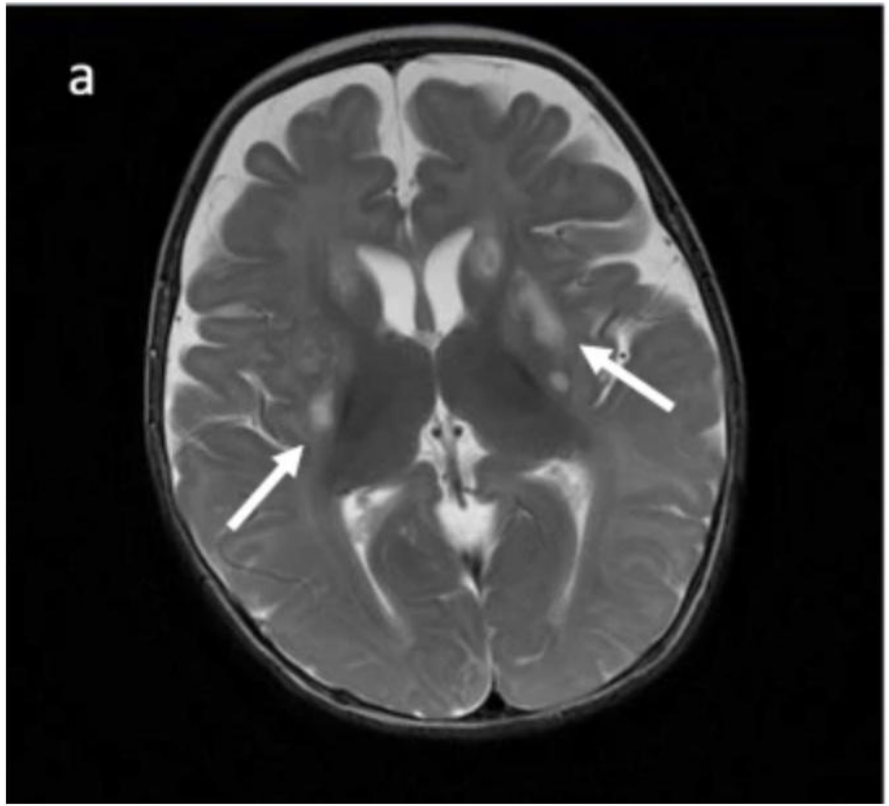
Seizures

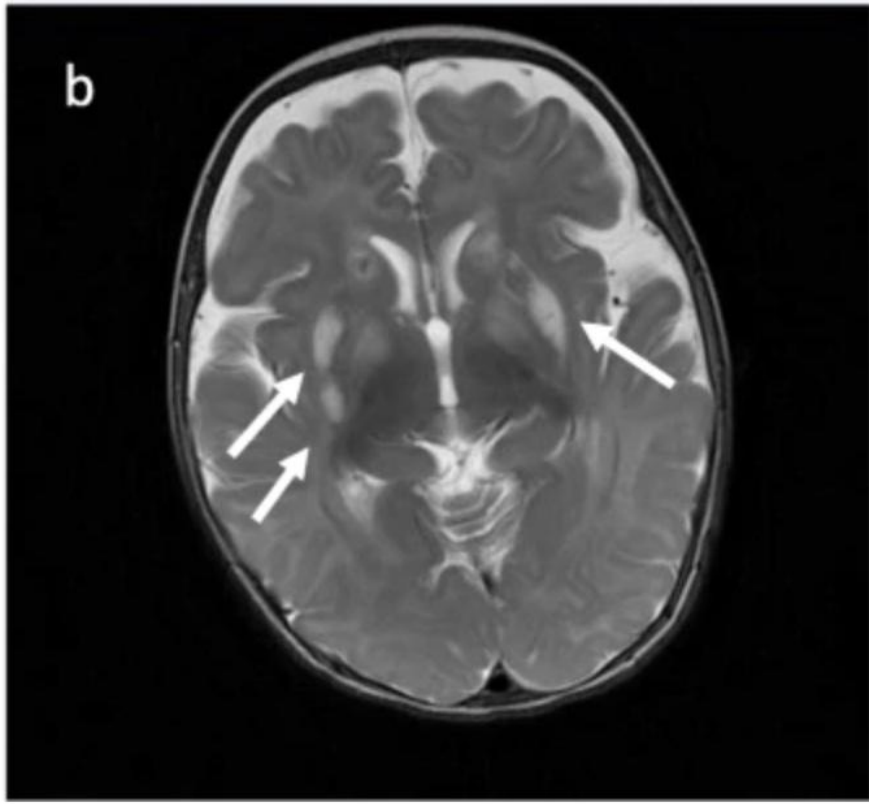
Dystonia

Weak suction or poor feeding

Respiratory abnormalities

Photos (9)





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