Patient journey PDH Deficiency

1 First Symptoms

… often occur in first years of life (sometimes prenatal findings) but later onset/milder presentations (especially ataxia) can be found

- Fetal growth restriction
- Microcephaly (primary + secondary)
- Facial dysmorphism
- **Developmental delay**
- **Lactic acidosis** w or w/o respiratory distress
- Hypotonia (axial), may be combined with limb hypertonia/ spasticity
- **Seizures** (focal and general)
- **Brain imaging**: asymmetric ventriculomegaly cerebral atrophy, T2 hyperintensity of the basal ganglia, structural brain abnormalities (e.g. corpus callosum dysgenesis), lactate peak in MR-spectroscopy
- **Movement disturbances** - poor balance, choreoathetosis, dystonia and/or ataxia
- **Sudden onset/ deterioration** in infection possible, MRI basal ganglia lesions, Leigh syndrome spectrum
- **Hearing** impairment/**visual** problems (optic atrophy, ptosis, nystagmus, strabismus)

Note: milder forms can present with just intermittent ataxia/dystonia (often fever or carbohydrate triggered) or periodic limb paralysis, paroxysmal exercise induced dystonia

2 Diagnosis

Age at diagnosis: vastly varying - can be antenatal, but is often made in later childhood, rarely in adulthood (median 45 months)

Clinical signs and symptoms: thorough clinical evaluation, assessment for developmental delay, movement disturbances (e.g. ataxia, dystonia, axonal neuropathy, spasticity) and seizures

Brain MRI findings: Assessment of structural alterations (Cerebral atrophy with asymmetric ventriculomegaly, dysgenesis of the corpus callosum) as well as suggestive findings: Leigh syndrome especially involving globi pallidi, MRS with lactate peak

Nerve conduction studies: may show peripheral neuropathy

Biochemical analysis /laboratory findings:
- Analysis of lactate/pyruvate in blood and/or CSF (hallmark: lactate↑ with normal L/P ratio)
- Low pyruvate dehydrogenase complex (PDC) enzyme activity

Molecular genetic testing:
Pathogenic variants in *PDHA1, PDHB, DLAT, DLD, PDHX, PDP1, PDK3,* ideally through comprehensive genomic testing to exclude alternative diagnoses mimicking PDH deficiency or causing secondary PDH deficiency

3 Treatment

Congenital lactic acidosis may need treatment with **sodium bicarbonate** +/- **dichloroacetate** (clinical trial in progress)

Ketogenic diet is the gold standard of long term therapy - improves seizure control +/- cognitive function and movement

Emergency regimen for intercurrent illness and perioperative management taking into account ketogenic therapy

High dose **thiamine,** riboflavin (in DLD E3) +/- other supplements (e.g. Coenzyme Q_{10},)

Anti-seizure medications
(caution valproate)

Supportive management:
- Physiotherapy / occupational therapy
- Dystonia management
- medical aids (wheelchair, walker, standing frames, transfer supports etc)
- Speech and language therapy, language support systems
- Enteral feeding if indicated
- Hip dysplasia management
- Scoliosis surgery
- Education: early intervention teams
- Psychological support for child and family

4 Monitoring

Monitoring of **development**, **clinical** + **nutritional status**, anthropometrics at regular intervals, special focus on assessment of:

- Growth: body weight, height & head circumference
- Development:
  - Motor function
  - Speech & language
  - Activities of daily living
  - Education
- Behaviour and psychiatric manifestations
- Seizure control
- Acid-base balance
- Nutritional status: vitamins & minerals
- Liver function in *DLD* (E3 def)
- Vision / ophthalmologic exam
- Hearing assessment
- Cardiac assessment (esp. *PDP1*)
- Bone health, scoliosis, hip dysplasia
- Dental exams
- Psychological wellbeing, sibling support
- Family support systems

5 Adult life

Coordinated transition into adult orientated health care systems
→ continuation of support by a specialist in PDH deficiency.

A prolonged **transition period** can be optimal to minimize difficulties in building a **new medical support network**

Involvement of patients in **medical decision making** – often additional lifelong support by parents/ legal guardian necessary

Sometimes a**djustment of ketogenic diet** required (e.g. lower ratio, modified Atkins) to keep adherence

Lifelong learning, continuation of special education, integrated work sites

If applicable: **financial** (governmental) assistance

Early access to **palliative care**

Be aware of **attenuated phenotypes** (e.g. presenting with intermittent movement disorder)

Family and social needs

- Ideally early diagnosis, treatment/follow up in a specialized center with multidisciplinary care: best involving metabolic specialists, neuropediatricians/neurologists, specialised dieticians, social worker, psychologists
- regular interdisciplinary check up's and care with specialists in epileptology, vision & sensory, orthopedics, gastroenterology etc. coordinated by a specialist in PDH deficiency
- family instruction for intercurrent illnesses / perioperative procedures, taking into account ketogenic diet
- additional support might be necessary to maintain activities of daily life, community involvement and improve quality of life for patients & caregivers
- access to early rehabilitation, physiotherapy, occupational therapy – access to community support
- early contact to family support groups if desired

This patient journey has been realized by the **PM-MD** MetabERN subnetwork group in collaboration with the **Freya Foundation**