WHEN TO CONSIDER PYRUVATE DEHYDROGENASE (PDH) DEFICIENCY

Primarily neurological involvement with a range of presentations
The severity and combination of symptoms vary depending on the patient and the nature of the deficiency[1]

Clinical signs

Early neurological decompensation
Occasional antenatal symptoms

Neonatal lactic acidosis with vomiting, feeding difficulties, **generalised hypotonia**, possible seizures and risk of early death

Sometimes associated with **intrauterine growth restriction** (IUGR)

Brain abnormalities, most commonly **agenesis of the corpus callosum,** Periventricular **cysts**

Progressive encephalopathy with episodes of deterioration (Leigh syndrome)
Often within the first 5 years of life, mainly in boys

Moderate to severe psychomotor developmental delay

Episodes of acute or subacute psychomotor regression, often triggered by intercurrent infections, associated with **hypotonia, dystonia**, ataxia and sometimes feeding and respiratory difficulties, which may progress to apnoea, impaired consciousness and sometimes death, with **basal ganglia abnormalities** on MRI

Encephalopathy of varying severity with fixed, non-progressive disability
More common in girls

Neonatal or acquired microcephaly

Neurodevelopmental disorder (beginning in the first months of life) with **axial hypotonia** and **spastic hemiplegia or quadriplegia**

Epilepsy is common

Paroxysmal episodes
With milder or even absent neurodevelopmental disorder

Intermittent ataxia triggered by carbohydrate-rich meals

Episodes of **dyskinesia,** choreoathetotic movements

Hemiplegia or episodic paralysis of a limb

Acute peripheral **neuropathy-like involvement**

Other manifestations
Dysmorphia[2]

Peripheral neuropathy

Rare ophthalmological involvement: optic atrophy, nystagmus, ptosis, ophthalmoplegia, strabismus

IUGR

Possible growth delay

Additional tests

Laboratory tests (abnormalities may be intermittent): Blood: Lactic acidosis, **Hyperpyruvicaemia and hyperlactataemia**, with normal or low **lactate-to-pyruvate ratio** (L/P around 10 and < 20)

CSF: **hyperpyruvorrhachia and hyperlactatorrhachia**, with normal or low **L/P ratio**

Brain MRI with spectroscopy: **Dysgenesis or agenesis of the corpus callosum**, periventricular or subependymal **cysts** (especially in early presentations), cerebral atrophy, ventriculomegaly, **Leigh syndrome:** T2 hyperintensity in the basal ganglia and sometimes in the brainstem and cerebellum; lactate peak on spectroscopy

Specialist assessment

Pyruvate dehydrogenase deficiency?

Specialist neuro-paediatric opinion

Specialist assessment
in parallel with the investigation of other possible differential diagnoses[3]

Lactate and pyruvate measurement in blood and CSF if not previously performed:
Hyperpyruvicaemia and hyperlactataemia, with normal or low **L/P ratio** (around 10 and < 20)
CSF: **hyperpyruvorrhachia and hyperlactatorrhachia**, with normal or low **L/P ratio**

Chromatography of plasma amino acids and urinary organic acids:
abnormalities that are sometimes suggestive and more or less specific

Confirmation by genetic testing +/- measurement of enzyme activity
(lymphocytes, fibroblasts)[4]

Referral to an Expert Centre:
Reference and Expert Centre for rare diseases:
https://www.filiere-g2m.fr/annuaire/

Specialist management coordinated by an Expert Centre

Genetic counselling and family screening at a specialist centre

Further information:
emergency protocols by symptom and/or disease:
https://www.filiere-g2m.fr/urgences

Specialist medical opinion and reference laboratory

[1] A genetically heterogeneous condition resulting from a deficiency of one of the subunits of the pyruvate dehydrogenase complex Both girls and boys may be affected
Most patients have an X-linked mutation in the *PDHA1* gene (which encodes the E1 alpha subunit); thus, neonatal or rapidly progressive forms are mostly described in boys.
[2] Long philtrum, thin upper lip, low-set ears
[3] Mitochondrial diseases, secondary PDH deficiency, other causes of encephalopathy with basal ganglia involvement, etc.
[4] The diagnostic confirmation strategy should be discussed with a specialist laboratory.

Filnemus Filière Neuromusculaire

Maladies rares Héréditaires du Métabolisme Filière nationale de santé