WHEN TO CONSIDER MELAS[1] OR A RELATED MITOCHONDRIAL DISEASE

MELAS is a clearly defined clinical form of mitochondrial disease, secondary to a mitochondrial DNA mutation.
It is characterised by the occurrence of neurological deficit episodes, usually beginning in young adulthood.
By extension, other clinical conditions are considered related to MELAS and may involve impairments of variable severity depending on the patient.
The clinical spectrum is broad, ranging from rare, very severe paediatric forms to moderate adult forms with several of the following symptoms:

Clinical signs

Stroke-like episodes

Acute neurological disorder mimicking a stroke, associated with headaches, nausea and vomiting

Impaired consciousness and/or **alertness** and/or **focal epilepsy** with or without **focal neurological deficits**, with **with MRI abnormalities suggestive of a pseudo-stroke**[4]

Chronic neurological and/or muscular involvement

Possible presentations at onset

Epilepsy (particularly epilepsia partialis continua)
Progressive cognitive and/or psychiatric disorders
Learning difficulties
Ptosis, ophthalmoplegia
Migraines
Peripheral neuropathy, muscle weakness, exercise intolerance

Frequent growth delay with short stature

Cardiac involvement

Hypertrophic cardiomyopathy, ventricular pre-excitation syndrome **(Wolff-Parkinson-White syndrome)**

Ophthalmological involvement

Retinal dystrophy, optic neuropathy

Gastrointestinal involvement

Gastroparesis, constipation, **chronic intestinal pseudo-obstruction (CIPO),** cyclic vomiting

Kidney involvement

Glomerular and/or tubular involvement

Sensorineural hearing loss[2]

Children or young adults, bilateral

Young-onset diabetes[2]

(20–40 years)

Diabetes with normal or low BMI, no autoantibodies, immediately or rapidly insulin-dependent

Endocrine disorders

Less common

Hypothyroidism, hypoparathyroidism, hypogonadism, rare growth hormone deficiencies

Additional tests

Laboratory tests: **Often elevated lactate (blood and CSF), with possible lactic acidosis and increased lactate/pyruvate ratio.** Sometimes: **elevated CPK**, abnormal liver function tests, signs of tubulopathy, glomerulopathy

Plasma amino acid and urinary organic acid chromatography: sometimes suggestive but non-specific abnormalities

Brain MRI with spectroscopy[3]: **pseudo-stroke or stroke-like lesions** [4], signal abnormalities in the **basal ganglia** including calcifications, sometimes atrophy, possible white matter involvement, **lactate peak** on spectroscopy

Specialist assessment

Mitochondrial disease related to MELAS?

Specialist assessment in collaboration with an expert centre
in parallel with the investigation of other possible differential diagnoses

Genetic confirmation (m.3243A>G, 80% of cases)
+/- muscle biopsy in certain specific contexts

Specialist advice from an Expert Centre:
Calisson: https://www.mito-calisson.fr or Carammel: https://carammel.org
Filnemus network: https://www.filnemus.fr/
or G2M network: https://www.filiere-g2m.fr/annuaire/

Initial assessment and specialist care coordinated by an Expert Centre

Genetic counselling, family screening in a specialist centre

Further information:
emergency protocols by symptom and/or disease: https://www.filiere-g2m.fr/urgences
and French National Authority for Health - National diagnostic and care protocol (PNDS) – Mitochondrial diseases related to MELAS (has-sante.fr)

Specialist medical opinion and reference laboratory

[1] MELAS: Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes
[2] The combination of deafness and diabetes is what defines Maternally Inherited Diabetes and Deafness (MIDD)
[3] Several types of involvement may occur, alone or in combination, and MRI may be normal without ruling out mitochondrial disease
[4] Lesions not confined to vascular territories: cortical, focal, sometimes multifocal, often parieto-occipital, with diffusion hyperintensity, hyperintensity on T2and FLAIR, hypointensity on T1, focal arterial spin labelling (ASL) hyperperfusion

Filnemus Filière Neuromusculaire
G2M Maladies rares Héréditaires du Métabolisme Filière nationale de santé