WHEN TO CONSIDER TANGO2 DEFICIENCY[1]

ONSET REVEALED BY ACUTE ATTACK OR CHRONIC ILLNESS, BOTH TYPES ARE OFTEN ASSOCIATED

2 TYPES OF ACUTE CONDITION: PAROXYSMAL NEUROLOGICAL EPISODES AND METABOLIC CRISES

Aggravating factors: +/- long fasting period, infection, general anaesthesia, intense physical exercise, dehydration

CHRONIC IMPAIRMENT

Type, association and severity of symptoms vary depending on patients

Clinical signs

Paroxysmal neurological episodes

May start in infancy
May last several minutes up to several hours, even days
Laboratory workup is generally normal during these episodes

Sudden hypotonia with loss of balance, falls and inability to get back up
Abnormal posture with tilting of head and body
Severe ataxia and dysarthria, dribbling
Agitation
Impaired consciousness
(confusion, lethargy, disorientation)

Metabolic crises with risk to life

Median age 3 years, different kinds of impairment possible, often associated

Rhabdomyolysis with very high CPK[2]

Weakness and muscle pain up **to complete functional incapacity,** no longer able to walk, psychomotor decline, comatose state, **dark-coloured urine**

Cardiac impairment[3]

Cardiac rhythm and/or conduction disorders: Long QT, Brugada pattern type 1, ventricular ectopia with risk of progression to ventricular arrhythmia, **ventricular tachycardia**or **torsade de pointe, cardiac arrest**
Cardiomyopathy, **heart failure**

Other impairments described in the literature

Severe hypoglycaemia on prolonged fasting
Liver damage: cytolysis, Reye syndrome
Hyperammonaemia with altered consciousness
Possible **pancreatitis** and adrenal failure

Neurological impairment

May be present before the symptoms become acute

Acquired microcephaly
Psychomotor delay
(walking and language delay)
Slight to moderate **intellectual disability**, up to severe encephalopathy
Pyramidal syndrome
Cerebellar syndrome (poor coordination when walking, speech problems, nasal or slowed-down voice)
Dystonia
Epilepsy
Sensorineural hearing loss

Hypothyroidism

Cardiac impairment

normal ECG
or occasionally long QT

Other

Intermittent strabismus, abnormal eye movements, rare cases of ocular atrophy

Additional tests

Very high CPK >10 000 IU/l, often >50 000 IU/l,
Elevated transaminases (AST, ALT)
Possible: **hypoglycaemia with ketosis or ketoacidosis,** moderate lactic acidosis, high ammonia levels,[4] hepatocellular insufficiency

ECG: Long QT, occasionally resembling Brugada pattern type 1 or other heart rhythm disorders
Cardiac ultrasound: potential altered heart function

Additional tests

Brain MRI: normal or generalised atrophy possible, sometimes affecting the pyramidal tracts

Hypothyroidism: elevated TSH and moderate decrease in thyroxine

Specialist workup

TANGO 2 deficiency?

Specialist workup in collaboration with a Centre of Excellence

Eliminate potential differential diagnoses[2]
There are no specific biomarkers that can be measured routinely
Confirmatory genetic analysis (*TANGO2* gene)

Specialist advice from a Centre of Excellence: Rare Disease Centre of Reference / Competence: *https://www.filiere-g2m.fr/annuaire*

Start the parallel treatment, urgently depending on how the condition is discovered

Refer to the emergency protocols for each symptom and/or disease: https://www.filiere-g2m.fr/urgences

Specialist treatment coordinated by a Centre of Excellence

Genetic counselling, family screening in a specialist centre

Specialist medical opinion and reference laboratory

[1]TANGO2= Transport and Golgi organisation protein 2 homologue.
[2]see the emergency protocol for rhabdomyolysis: https://www.filiere-g2m.fr/urgences.
[3]Warning: the cardiac signs may be out of sync with the other metabolic decompensation symptoms, and occur at a later time, especially when CPK levels drop.
[4]Pay attention to sample-taking conditions. Always perform tests but do not necessarily wait for test results to start treatment. Standard norms (may vary depending on the laboratories): Neonates: ammonia <100 µmol/L, Non-neonates: ammonia <50 µmol/L, see: emergency protocol for hyperammoniaemia: https://www.filiere-g2m.fr/urgences.

Maladies rares Héréditaires du Métabolisme
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