New causes of persistent or recurrent 3-methylglutaconic aciduria – expanding the differential diagnosis of secondary 3-MGA-uria

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Introduction

3-methylglutaconic aciduria (3-MGA-uria) can be a major finding when persistent, recurrent, isolated or significantly elevated.

All secondary 3-MGA-urias result from mutation-induced effects on electron transport chain (ETC)-related energy production, causing an increase in the intra-mitochondrial NADH / NAD+ ratio such that inhibition of the Krebs cycle enzymes isocitrate dehydrogenase and ketoglutarate dehydrogenase occurs.

In non hepatic tissues including skeletal muscle, heart and brain, this metabolic impediment results in redirection of mitochondrial acetyl CoA toward production of 3-MGA.

Here we report four unrelated new causes of significant 3-MGA-uria.
Results

Previously healthy 4 year-old female with two cardiorespiratory arrests after respiratory viral illness at the age of 2 and 3 years old, asymptomatic in between.

- **ISD11 mitochondrial iron-sulfur cluster deficiency (published)**
  - Moderate excretion of 3-MGA (154 µmol/mmol creatinine) and mild excretion of 3-OH-IVA and 3-HMG.
  - NGS for mitochondrial disorders
  - Novel pathogenic variant in homosygosity in the LYRM4 gene [p.Tyr31Cys (c.92A>G)]
  - Functional studies in the skeletal muscle
  - Combined deficiency of the mithocondrial respiratory chain (I, II and IV complexes).

**Urinary organic acids during acute events**

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Previously healthy 5-years-old female with two episodes of ataxia and prostration at the age of 2 and 3 years old, asymptomatic between crisis.

- Consistent isolated excretion of 3-MGA with 14.2 µmol/mmol creatinine (NR <19 µmol/mmol creatinine).
- NGS for mitochondrial disorders
- Two pathogenic variants in heterozigosity in the SLC19A3 gene [described c.980-14A>G and novel p. Trp59 (c.177G>A)] - dysfunction syndrome in thiamine type 2 metabolism.
- Biotin and thiamine supplementation: significant improvement.

**Thiamine-responsive basal ganglia disease (SLC19A3).**
### Results

#### III

5-months-old male with two cardiorespiratory arrests after severe dehydration (1 month-old) and viral illness (4 months-old) followed by acquired microcephaly and failure to thrive without cardiomyopathy.

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<tr>
<th>Urinary organic acids</th>
<th>NGS for mitochondrial disorders</th>
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<tbody>
<tr>
<td>Both episodes had moderate excretion of 3-MGA (35.2 µmol/mmol creat.), 3-HMG and 4-hydroxyphenyllactate (both some days after crises).</td>
<td>two novel pathogenic variants in heterozigosity in the COX15 gene [pArg183His (c.548G&gt;A) and c.*24T&gt;C].</td>
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**COX15 deficiency**

#### IV

Ex-premature (33 weeks), 12-months-old male with abducens nerve palsy, significant bilateral peritrigonal white matter hypersignal.

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<th>Urinary organic acids</th>
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<td>persistent excretion of 3-MGA with 28-38.3 µmol/mmol creat., 3-HMG and tiglyglycine.</td>
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He is thriving with normal development.

**Extensive genetic studies failed to provide a diagnosis.**
3-MGA-uria, often associated with 3-methylglutaric aciduria, is a relatively common finding in patients with metabolic disorders in general.

Patients with 3-MGA-uria can only display consistently elevated levels of 3-MGA when placed under metabolic challenge.

Persistent, isolated or recurrent 3-MGA-uria than may only be present in life-threatening crisis should elicit a wide investigation and follow-up.

These cases widen the range of possible underlying causes of consistent 3-MGA-uria corroborating mitochondrial dysfunction as a common denominator.