c.683 <T (Pro 228Leu) mutation in KARS gene is associated to hypoglycemia and liver involvement

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KARS gene encodes both the cytosolic and mitochondrial isoforms of lysyl-t-RNA synthetases, which are ubiquitous enzymes involved in organellar translation.

The mutated cytosolic isoform results in an abnormal synthesis of respiratory chain components, leading to a mitochondrial dysfunction.

The clinical phenotypes of KARS mutations reported in the literature are dominated by neurological and neurosensory impairment.

We report two unrelated cases of KARS mutations characterized by their singular presentation.
Case 1: AK, 3 Years old boy

Medical History:
Non consanguineous parents; Normal psychomotor development

Onset: 2 Years 5 months

- **Recurrent acute attacks** triggered by: fever, vomiting or anorexia

  Trouble of consciousness

  Hepatomegaly + cytolysis (1,5-2 x UNV), and liver failure PT=56%,

  Hypoglycemia (0,2-0,4 g/l), ketonuria (++)

  Acidosis (pH=7,2, HCO3-=8,1, AG=26)

  Lactates ↘ (3,6 → 7,7 mmol/l)

  OA profile in urine: ↑ lactate + 3OH butyrate

- **Previous episode of acute pancreatitis**

- **No evidence of neuro-sensory or muscular impairment**: Brain MRI, Echocardiography, ENMG, CK: normal
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**Case 2: AS, 2 years old girl**

- **Medical History:**
  - Consanguineous marriage, **Early deaths** (uncles)
  - Normal psychomotor development

- **Onset: age= 19 months**

- **Susceptibility to infections**

- **Recurrent hypoglycemia**
  - Acidosis, Ketonuria = (+)
  - Lactate=2,37 mmol/l → 3,4 mmol/l
  - Plasma AA profile: Normal,
  - OA in urine: ↗ 3-OH butyrate

- **Hepatomegaly** (Transient)
  - Cytolysis > 20 x UNV, normal PT, CK ↗=380

- **Neurologic impairment ++**
  - Pseudostroke
  - Ataxia, hypotonia, dysarthra, dystonia
  - Nystagmus, Fatigability when walking
  - Brain MRI, ENMG and Echocardiography: normal
Fructose 1,6-diphosphatase deficiency
DLD deficiency
FAO oxidation defects (+/-)

DIAGNOSIS

Homozygoty for the variant c.683 C>T (p.Pro228Leu) in KARS gene

Case 1: Whole exome sequencing
Case 2: NGS (Panel Mitochondriopathy, France)

CONCLUSION

Through these two cases, we pointed out a particular presentation of c.683 >T KARS gene mutation, not reported previously: recurrent hypoglycemia + hepatic involvement.

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