UMPS deficiency case, the importance of multi-omics diagnostics

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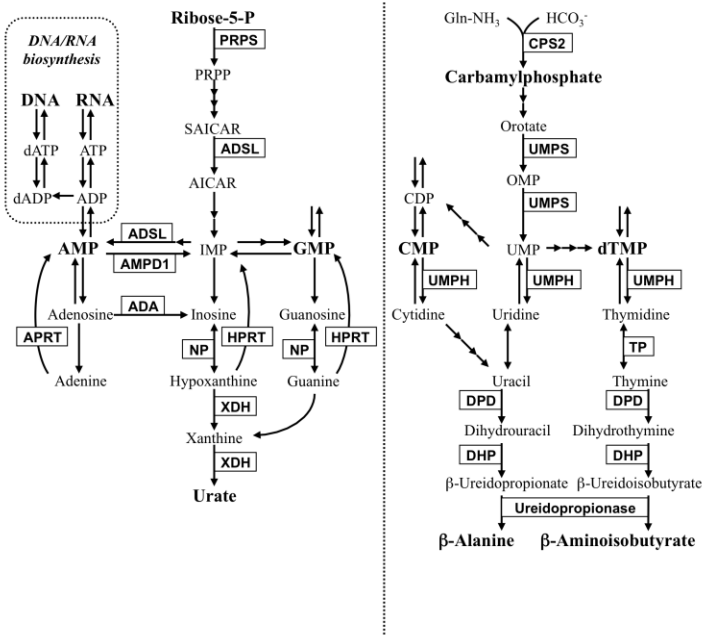
Radboudumc

UMPS: Uridine Monophosphate Synthase Deficency

Radboudumc

Disorder in the pyrimidine metabolism



case

- 3 year old boy
- History
  - 2nd child of non consanguineous parents, one miscarriage
  - Prematurely born 30 weeks
  - Congenital urethral valves, surgically treated
  - Congenital normocytic transfusion dependent anemia, also a mild leucocytopenia with neutropenia. Blood transfusions every 5-7 weeks
  - 3 months: nefrocalcinosis/lithiasis and dilated pyelum (left)

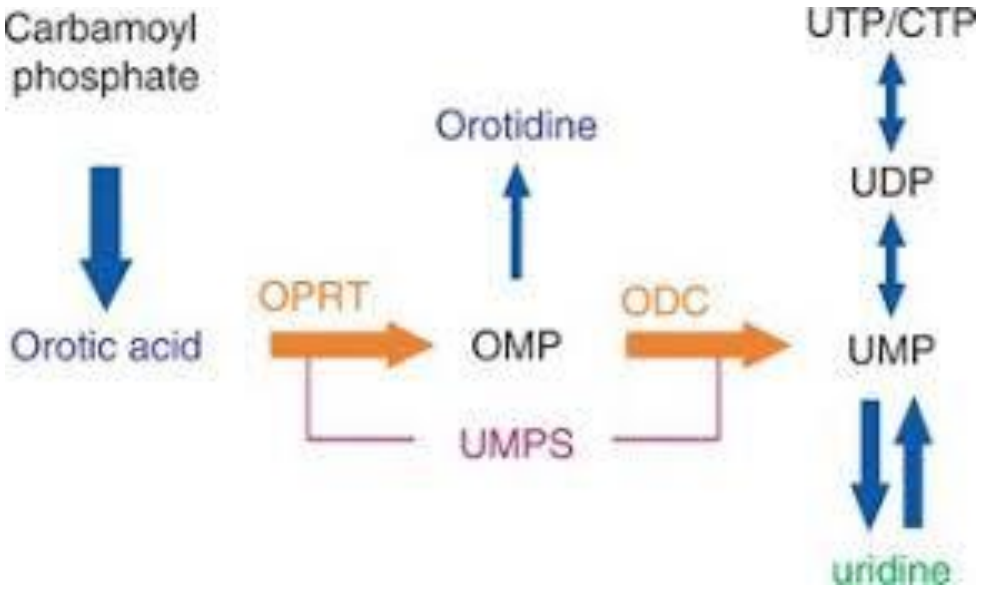
- 2 years acute kidney failure due to obstruction by kidney stones
- Motor and speech development adequate
- Height -1.2 SD and weight for height -0.8 SD

- Diagnostic workup congenital anemia, ringsideroblasts without hemolysis
- Karyotyping normal 46 XY
- Exome sequencing anemia panels, trio WES

- Result trio WES: heterozygous mutation in SEC23B, associated with dyserythropoietic anemia type II (CSAII) in case of bi-allelic mutations
- After 2 years of diagnostics it was decided to do metabolic screening

- Metabolic screening
- UOA and purine/pyrimidine analysis: very high orotic acid: 3404 umol/mmol kreat (ref 0-4) without indication in the serum amino acids for a urea cycle disorder

- Diagnosis: UMPS deficiency/ hereditairy orotic aciduria


Carbamoyl phosphate
Orotic acid
OPRT
Orotidine
OMP
UMPS
ODC
UTP/CTP
UDP
UMP
uridine

UMPS deficiency/ hereditairy orotic aciduria

- Kidney stones due to orotic acid stones
- Anemia due to decreased production of UMP, leading to impairment cell division/erytropoiesis
- Impairment growth/development

- Enzyme analysis erytrocytes not possible due to frequent blood transfusions, fibroblasts?

- Re analysis trio WES:
  - UMPS: 866A>G (Asp289Gly) and 1064A>C (Gln355Pro), compound heterozygous, first classified as class 2/3. Predicted non pathogenic by mutation predictive software, although not mentioned in sequence variant databases. Not mentioned in literature.

- Kidney stone analysis orotic acid stone
- Enzyme analysis: UMPS activity in erytrocytes: deficient

Treatment

- 1969 Becroft er al: Hereditairy orotic aciduria: long term therapy with uridine and a trial of uracil
- 2014 Shanti Balasubramaniam et al JIMD, Inborn errors of pyridmidine metabolism, clinical update and therapy
- Trial uridine tri acetate (Xuriden), registered in US, expensive (800.000 euro's per year?), not registered in the Netherlands
- 15 cases reported, in the Netherlands in the meantime 2 patients

- Radboud pharmacy: permission import IGJ, but route difficult and second step financial compensation insurance company

- Uridine: 150-300 mg/kg
- Xuriden 60 mg/kg, max 120 mg/kg

- 89 euro for 150 gram
- Food supplement good for concentration

- Started on 60 mg/kg in january 2020
- From blood transfusions every 5-7 weeks, no blood transfusions needed now for one year
- Reticulocytes and leucocytes increased

- Much more energy, eating is better, growth improved
- But orotic acid levels still high, effect on kidney has to be seen
- Higher dose uridine

Summary

- Metabolic screening really here added quality of life to this patient
  - Combination of Metabolic diagnostics and data of whole exome sequencing has lead to the diagnosis

- Impressive effect of uridine therapy

- Issues
- GMP manufactered product in the Netherlands
- Financial compensation by insurance company

Thank you for your attention

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