Ornithine Transcarbamylase Deficiency

Newborn Screening TAC Meeting

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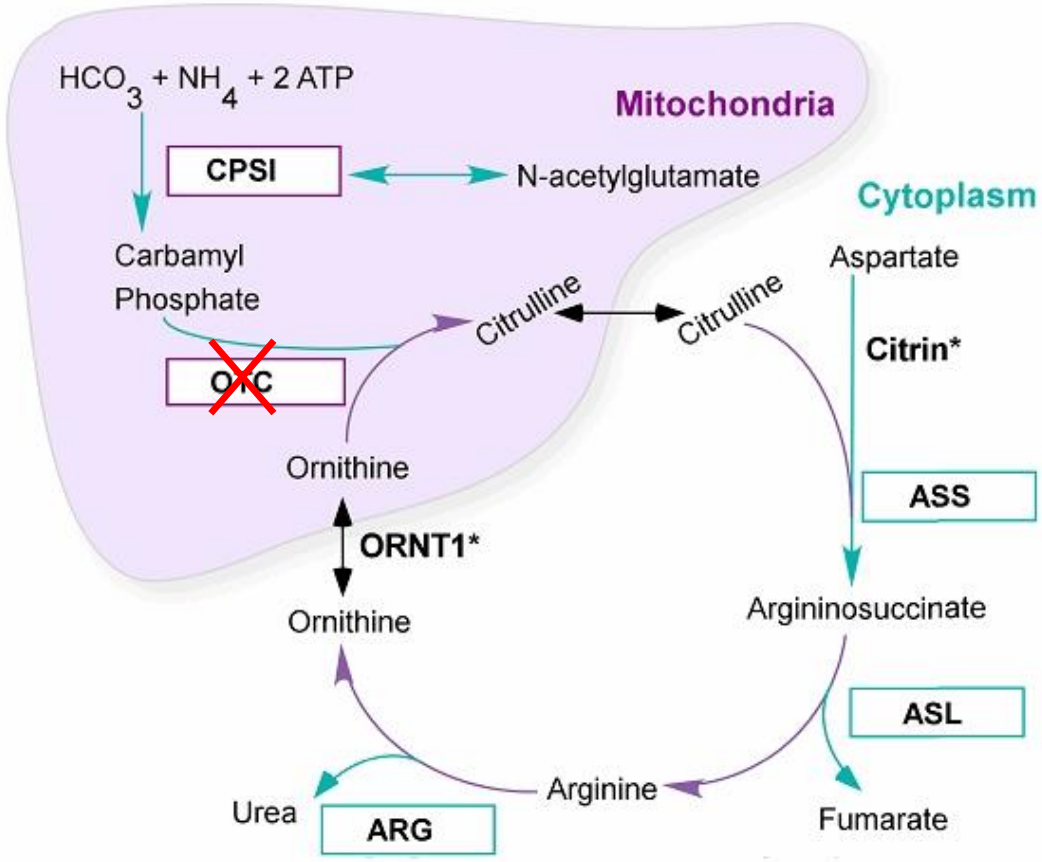
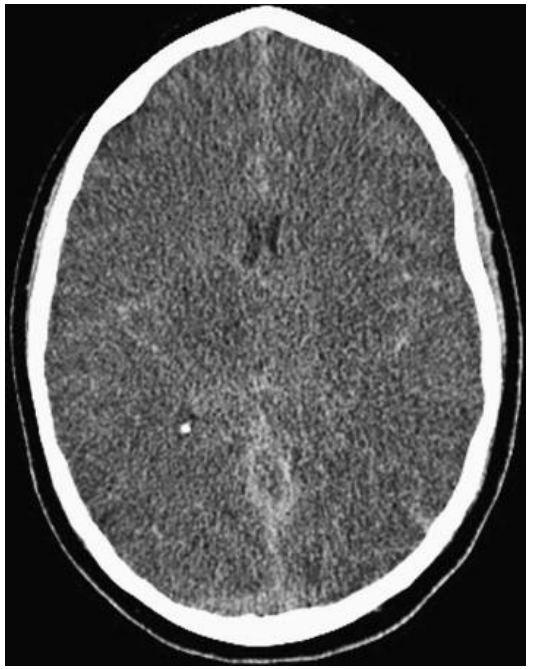
OTC Deficiency

- Urea cycle – the body's way of eliminating waste nitrogen
- Ammonia is produced from protein breakdown
- Incidence 1/17,000 in U.S.
- X-linked



Long-term outcomes in Ornithine Transcarbamylase deficiency: a series of 90 patients. Orphanet J Rare Dis. 2015 May 10;10:58.

Hyperammonemia



- Cerebral edema
- Triggers
  - Birth
  - Infection (flu, stomach virus, common cold)
  - Fever
  - Fasting
  - Medications (high dose steroids, valproic acid, L-asparaginase, etc.)
  - High protein load
  - Prolonged or intense exercise

OTC Clinical Presentation

- Neonatal (30%) – poor feeding, vomiting, lethargy, hyperventilation, seizures, coma, death
  - Mortality 74-90%
- Childhood (60%) – poor growth, developmental delay, hypotonia, episodic encephalopathy with ataxia, seizures
- Adolescent/adult (10%) – chronic neurological or psychiatric symptoms, behavioral problems, migraines, episodes of disorientation or psychosis triggered by high protein intake or stress, protein aversion

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Table 1 Epidemiological characteristics of the patients

	Neonates	Group 1 m-16y	Group >16y
Number of cases	27	52	11
Males	22	21	5
females	5	31	6
Number of deceased	20	7	1
at diagnosis	13	5	1
during follow up	7	2	0
Number of decompensations per patient (and relative to mean length of follow-up)*	6,2 (1.0/yr)	2,5 (1/10 yrs)	1,4 (<1/20 yrs)
Neurological score (IQ) at last follow up, N > 80	90	92	Normal socio-professional insertion
Mean peak plasma ammonia at diagnosis (μmol/L), N < 50 μmol/L	960	500	
Mean plasma glutamine at diagnosis (μmol/L), N: 530 +/- 81 μmol/L	4110	1000	
Plasma citrulline at diagnosis (μmol/L), N: 26+/-8 μmol/L	5	15	14

*Only the patients that survived beyond neonatal life were included.

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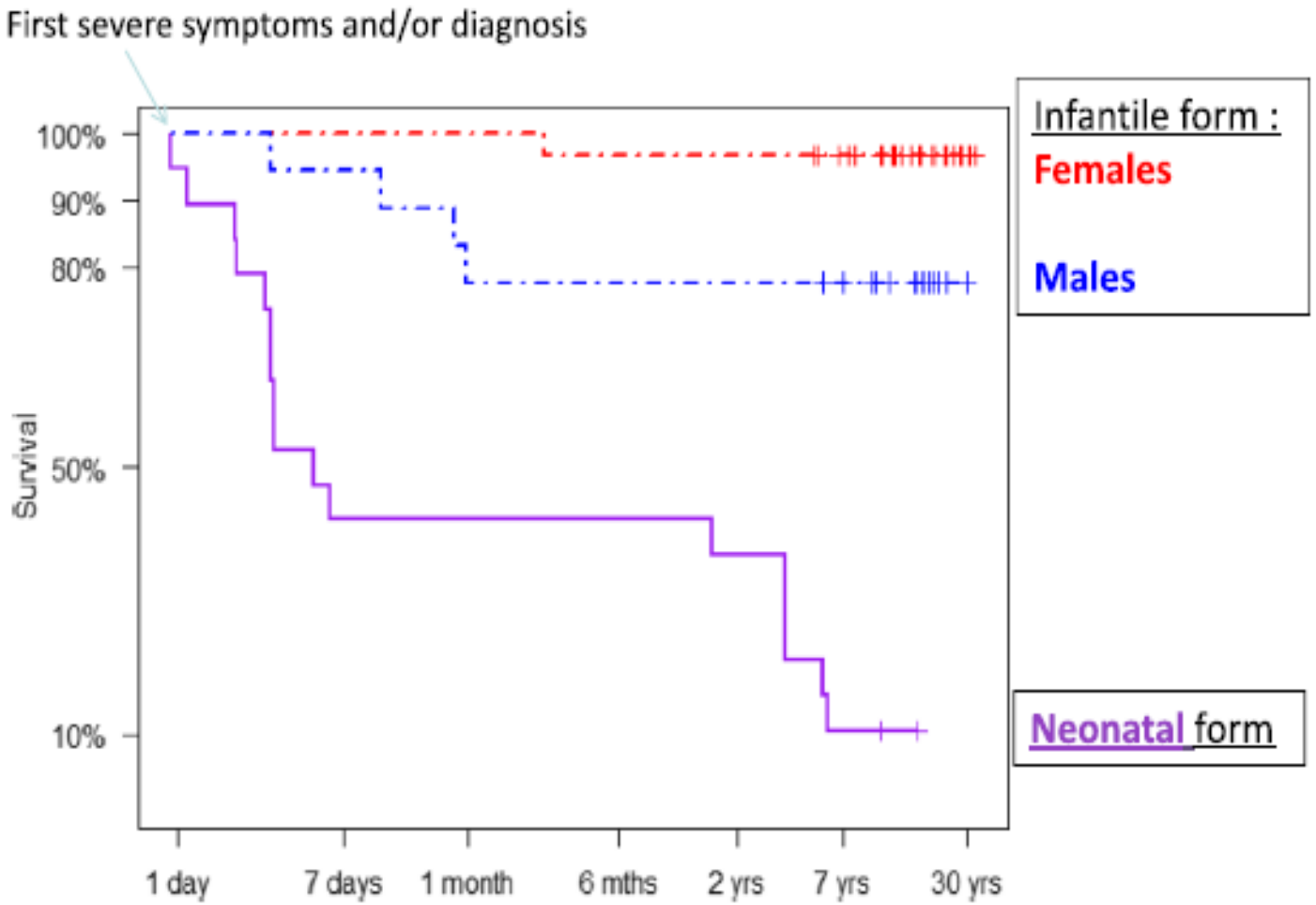

Figure 1 Survival of OTCD patients by age of onset. Comparison of survival between the 1 mth-16 y and neonatal group. In the 1 mth-16 y group, the "critical" period (risk of death) is that between the first severe symptoms and diagnosis. In the neonatal form, there are two high-risk age intervals: the first days of life and the period between 1 and 7 years of age.

OTC Deficiency

- Survival
  - 9% if ammonia >1000
  - 90% if ammonia <500
- Children treated from birth (prenatal diagnosis) have better outcome as management of the first crisis is crucial
- In adults, death may occur during the first episode of decompensation if diagnosis unknown

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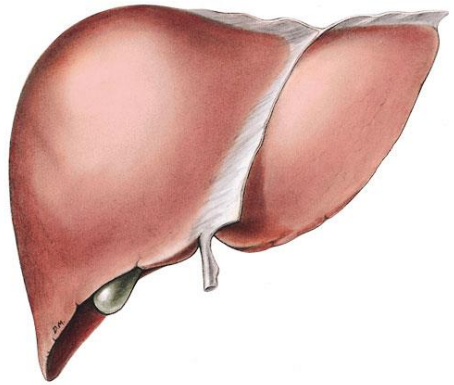
Management

- Protein restriction
  - Based on age
  - Intact protein and essential amino acids
- Nitrogen scavengers
  - Sodium benzoate, sodium phenylbutyrate
  - Glycerol phenylbutyrate (Ravicti)
  - Ammonul (IV)
- Replenish urea cycle intermediates – arginine or citrulline
- For emergencies
  - Caloric support – high dextrose IV fluids, lipids
  - Hemodialysis
- Other – G-tube, early intervention services

Liver Transplantation



- Corrects the metabolic defect
- Generally performed by 6 months in severe form
- Allows liberalization of diet
- Neurocognitive deficits remain
- Long-term immunosuppression, monitoring labs
- 90% survival at 5 years

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Cognitive and Behavioural Outcomes of Paediatric Liver Transplantation for Ornithine Transcarbamylase Deficiency. JIMD Rep. 2019;43:19-25.
Early orthotopic liver transplantation in urea cycle defects: follow up of a developmental outcome study. Mol Genet Metab. 2010;100 Suppl 1(Suppl 1):S84-7.
The role of orthotopic liver transplantation in the treatment of ornithine transcarbamylase deficiency. Liver Transpl Surg. 1998 Sep;4(5):350-4.