

# Encephalopathy

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ד"ר אילת פרטוש עבו

מכון גסטרו

בני ציון

# Case presentation

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- Born on June 1974
- Moderate global developmental delay was noted early in life
- 12 years of age: Epilepsy – was commenced with Valproic acid and Carbamazepine
- At 41 years of age: moderate intellectual disability, seizures well controlled
- Recurrent hospitalizations to Neuro. Dep. since 11/2015
  - confusion, restlessness, changes of behavior (aggression, irritability, and hyperactivity), lethargy

# Physical examination

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- Intermittent weakness
- Normal abdominal examination

# Medication list

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- CARBAMAZEPINE
- VIMPAT (lacosamide)– 4/2015
- KEPPRA (levetiracetam)
- DEPALEPT (valproate)

# Blood work

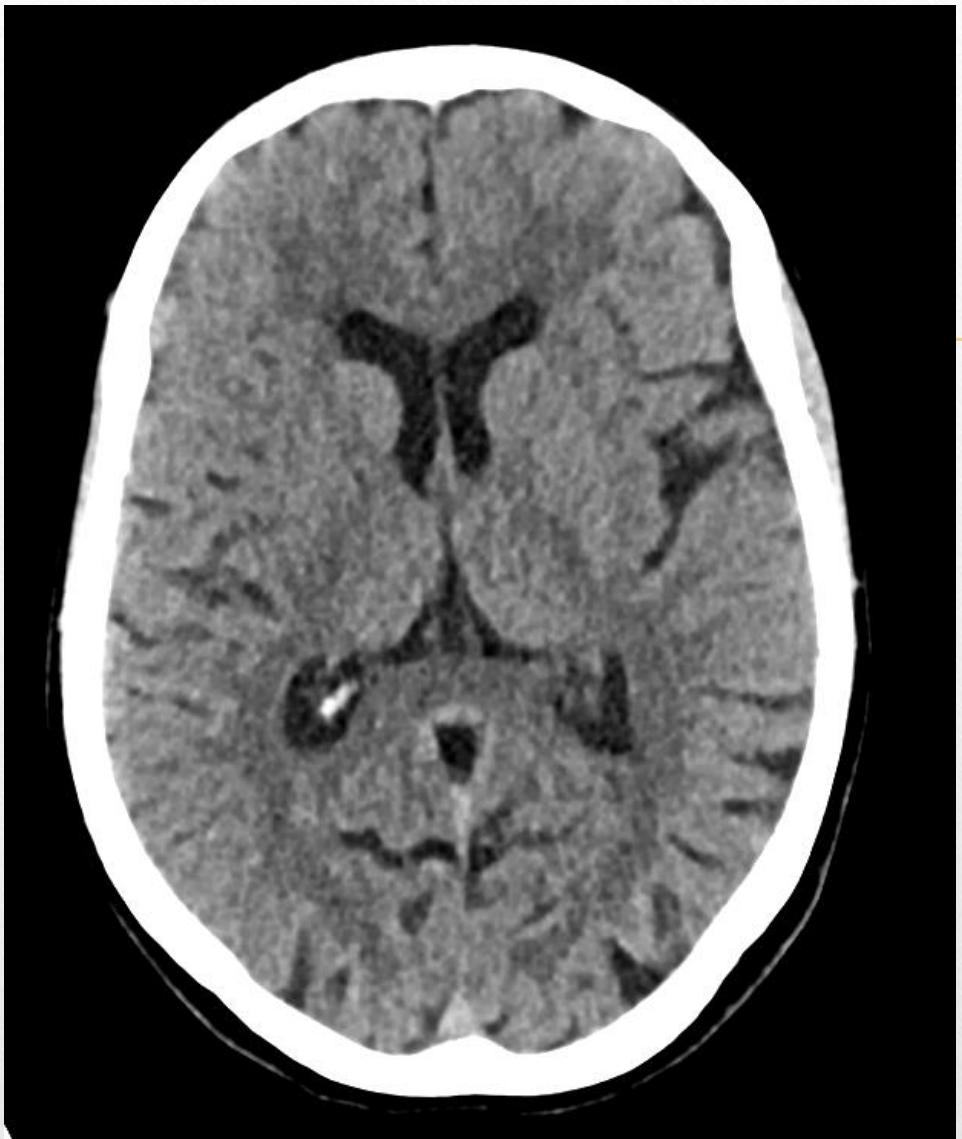
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- Normal Glucose
- LFT:
  - normal AST, ALT, GGT.
  - ALP – mildly elevated
  - BILIRUBIN – not elevated
- ALBUMIN – 3.2-2.7
- CBC: HG 13, PLT 150K, WBC 6.5
- COAG: INR – 1
- VALPROIC ACID – not toxic

# EEG

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- Encephalopathic tracing, general deceleration
- Triphasic waves
- No convulsive activity



CT

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# Lumbar Puncture

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- No pleocytosis
- Normal glucose and protein
- Sterile CSF culture

# Medication list

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- TEGRETOL
  - VIMPAT – 4/2015
  - KEPPRA
  - DEPALEPT
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- EPANUTIN – 27/11/15

# Hyperammonemic Encephalopathy

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Encephalopathic EEG

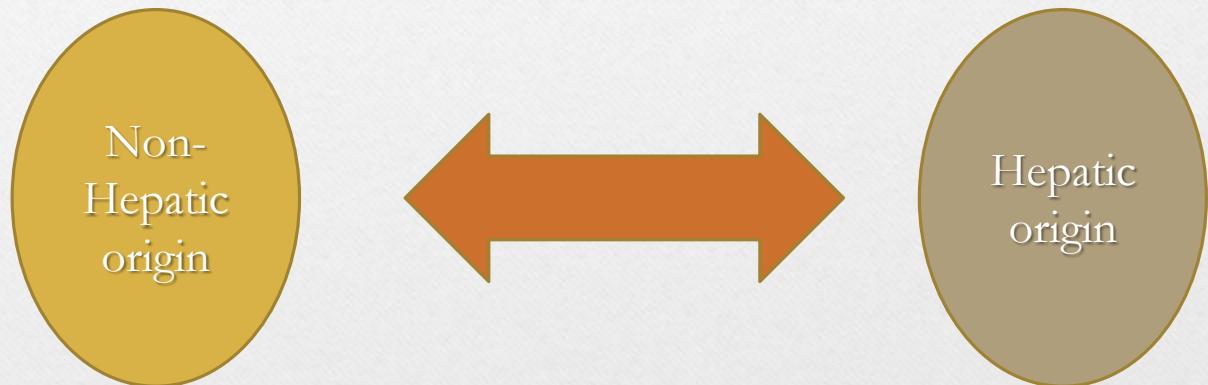
Lethargy

ammonia

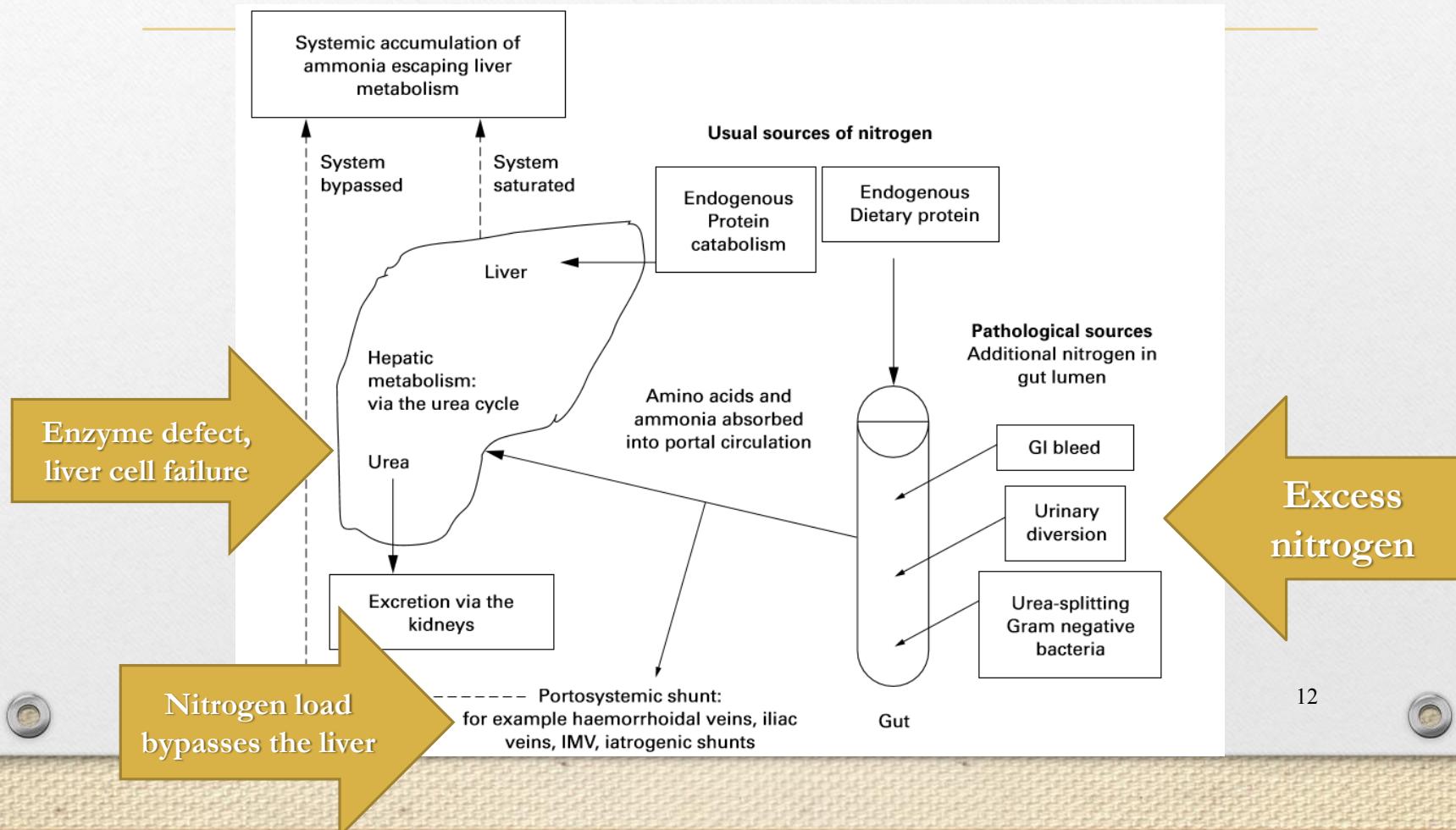
myoclonus

# Hyperammonemic Encephalopathy

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# primary sources and pathways of ammonia production and secretion



# Hyperammonemic Encephalopathy

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- Hepatic
  - Type A: acute liver failure
  - Type B: Portosystemic shunts (in the absence of liver disease)
  - Type C: chronic & end-stage liver disease and portal hypertension

# Further investigation...

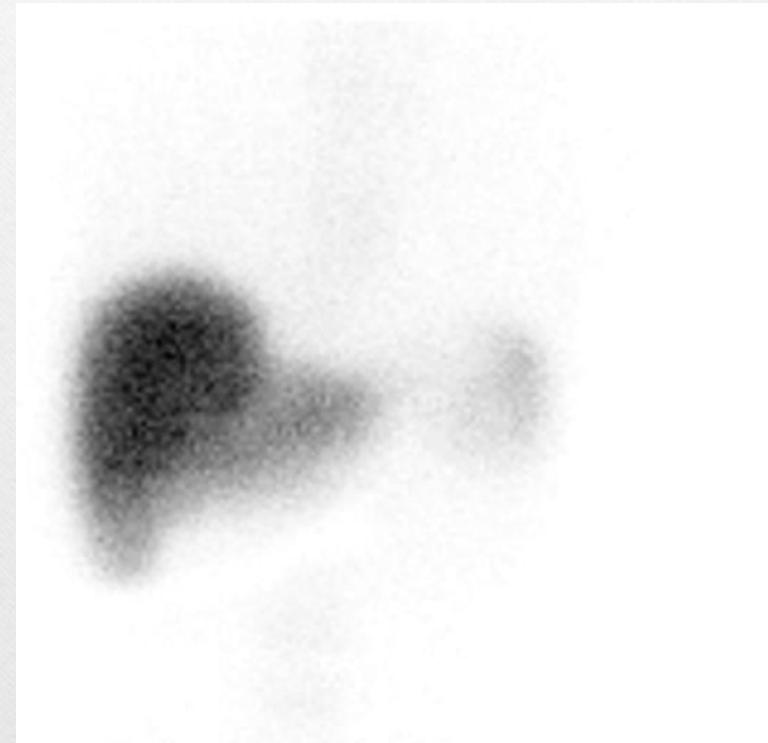
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- Serologic tests
  - Viral
  - Immunologic
- US
  - Doppler
- CT – chest, abdomen, pelvis
  - Normal liver
  - No evidence for shunts

# Further investigation...

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- Liver and spleen scintigraphy
  - No colloid shift



# Interim summation

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- Non-hepatic hyperammonemic encephalopathy
- No evidence of liver disease
- What next?

# Additional details on Hx:

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- born on June 1974
- The first child of **first-cousins** Muslim Bedouin parents
- Moderate global developmental delay was noted early in life
- 12 years of age: Epilepsy – was commenced with Valproic acid and Carbamazepine
- At 41 years of age: moderate intellectual disability, seizures well controlled
- Diet: **aversion to sugars, prefers high-protein food**

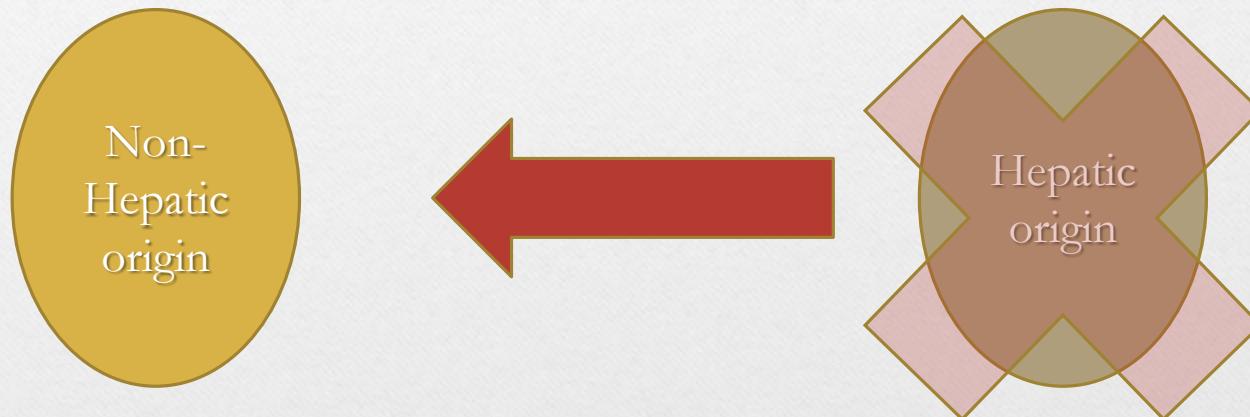
# Additional labs:

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- Bacteruria, leukocyturia
- *Citrobacter Koseri*

# Hyperammonemic Encephalopathy

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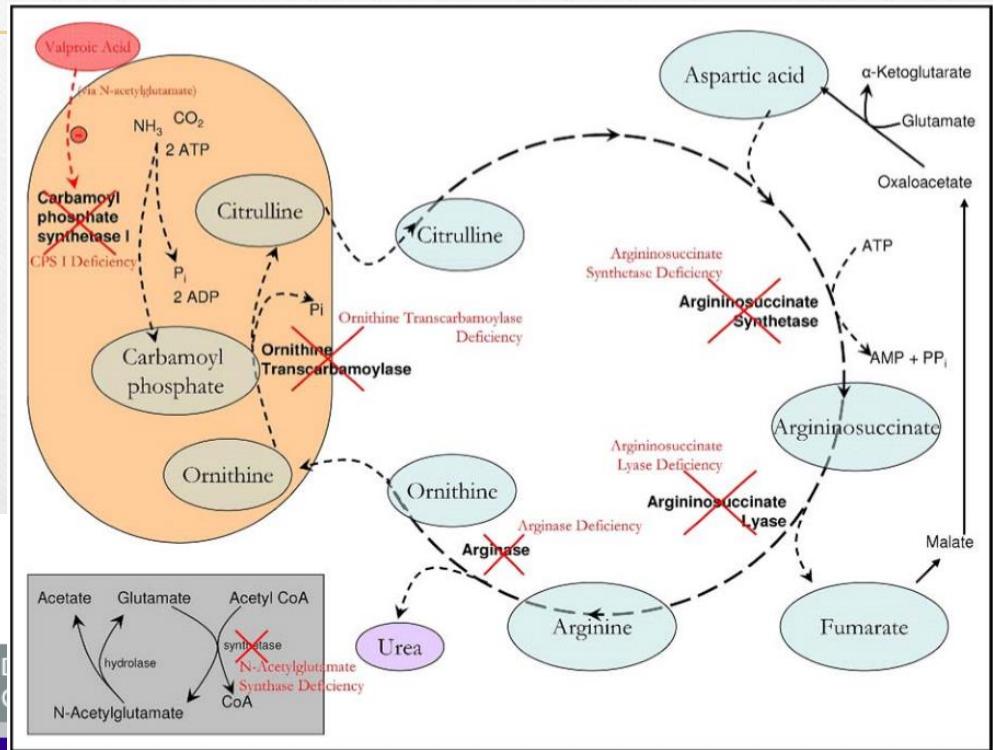


# Hyperammonemic Encephalopathy non-Hepatic

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- GI Bleeding
- Inborn errors of metabolism
  - Proline metabolism disorders
  - Urea cycle defects
- medications/toxins
  - Alcohol
  - Diuretics
  - hyperalimentation
  - Narcotics
  - Valproic acid
- Muscle exertion and ischemia
- Bowel or Urinary tract infections
- Technique and conditions of blood sampling
- Cigarette smoking

# Non Hepatic Hyperammonemia Valproic acid toxicity?



TRUVEN HEALTH ANALYTICS  
MICROMEDEX® SOLUTIONS

Home Drug Interactions IV Compatibility Drug ID

## Drug-Drug Interactions (1)

Drugs:

Severity:

Summary:

PHENYTOIN – VALPROIC ACID



Moderate

Concurrent use of PHENYTOIN and VALPROIC ACID may result in altered valproate levels or altered phenytoin levels.

# Non Hepatic Hyperammonemia

## Valproic acid toxicity?

ammonia µg/L	ethanol µg/dL	
19-87		
*141*		08:16 29/12/2015
*374*		07:18 30/12/2015
46		08:14 31/12/2015
75		07:52 03/01/2016
*431*		15:26 05/01/2016
80		08:18 06/01/2016
80		08:19 07/01/2016
*253*		15:35 14/01/2016
76		06:03 15/01/2016

STOP: VIMPAT, VALPROATE,  
PHENYTOIN

No convulsions were documented

Ammonia levels – intermittently elevated

Stop VALPROIC ACID

Stop PHENYTOIN

# Non Hepatic Hyperammonemia

## Urinary tract infection?

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- Urease producing bacteria
  - *Proteus mirabilis*
  - *Corynebacterium* species
  - *Helicobacter pylori*
  - *Klebsiella* sp.
  - *Morganella* sp.
- Systemic Reabsorption of ammonia
- Mild infection

# What next?

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# Non Hepatic Hyperammonemia

## Errors in metabolism?

Susp. Urea  
cycle dis.

d/t valproate?

low-protein  
containing diet

- הומצאות אמינוות בדם:

- ציטרולין, ארגinine, אוריגנtin, ליzin ותראונין מעל הנורמה
- גלוטמין מתחת לנורמה

- הומצאות אמינוות בשתן:
- הפרשת גליקין מוגברת

# Patient outcomes

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- The following morning she was found in a deep coma with kussmaul breathing
- Severe hyperglycemia,hypertriglyceridemia, hypernatremia, hypokalemia, metabolic acidosis and hyperammonemia

**What did we do wrong?**



# Non Hepatic Hyperammonemia Errors in metabolism?

Susp. Urea  
cycle dis.



- הומצאות אמינוות בדם:
  - ציטרולין, ארגinine, אוריגנtin, ליzin ותראוניין מעל הנורמה
  - גלוטמין מתחת לנורמה
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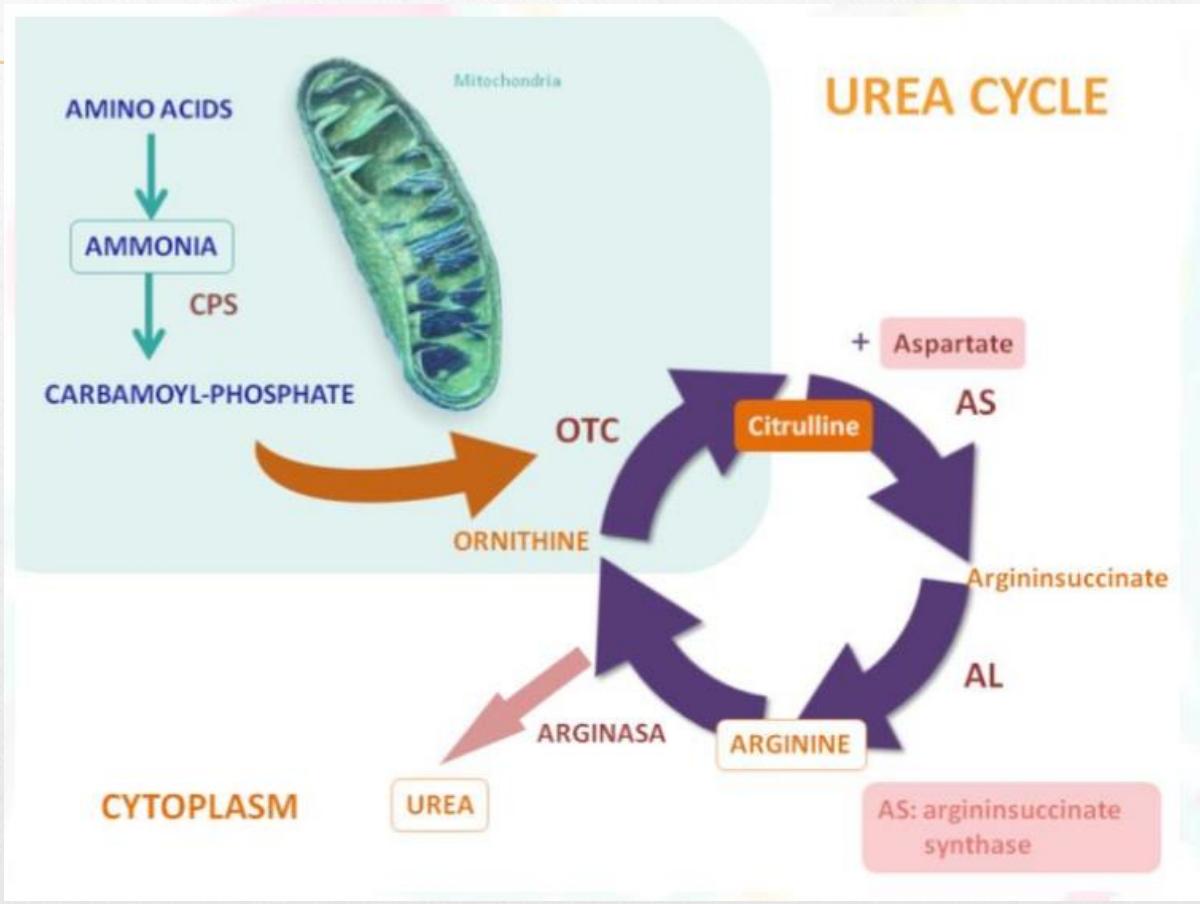
Type II  
Citrullinaemia

# Citrin Deficiency

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- Inherited metabolic dis.
- Mutations in the SLC25A13 gene encoding **mitochondrial transporter citrin**
- **Aspartate/glutamate transporter**

# Citrin Deficiency

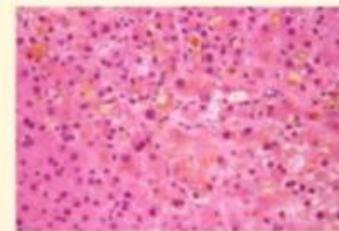


# Citrin Deficiency

## Clinical symptoms of citrin deficiency

NICCD type

Neonatal hepatic cholestasis



FTTDCD type



Hypoglycemia



Growth retardation

CTLN2 type



Aggressiveness



Delirium

# Type II (adult onset) citrullinaemia

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- AR, Male>female
- age of onset: 11 to 72 years
- “Hepatocerebral disease”
- **aversion to carbohydrates**

# Treatment

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- **low carbohydrate diet**, arginine supplementation, sodium citrate, sodium benzoate, lactulose, and branched chain amino acid infusion.
- **Liver transplantation**

**CTLN2 type**

Protein-rich  
Lactose-free diet  
MCT

Liver transplantation



## Circle of life



- Early onset IEM (inborn error of metabolism) reaching adulthood
- Adult patients with early onset IEM for whom diagnosis was missed
- Late-onset forms of IEM presenting initially in adulthood

# Take Home Message

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- Hyperammonemia – Not necessarily hepatic origin
- Consider IEM when:
  - Absence of hepatic/portal etiology
  - Family history
  - Food aversion

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*Thank You For  
Listening*