

Hyperammonemia and inborn errors of metabolism (IEMs):

Known and novel applications for differential diagnosis

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Point of discussion

- **Introduction**
 - Definition
 - Primary vs. secondary hyperammonemia
- **Clinical presentation**
- **Biochemical background**
- **Hyperammonemia and inborn errors of metabolism**
- **Differential diagnosis of Hyperammonemia**
- **Treatment options**
- **Summary**

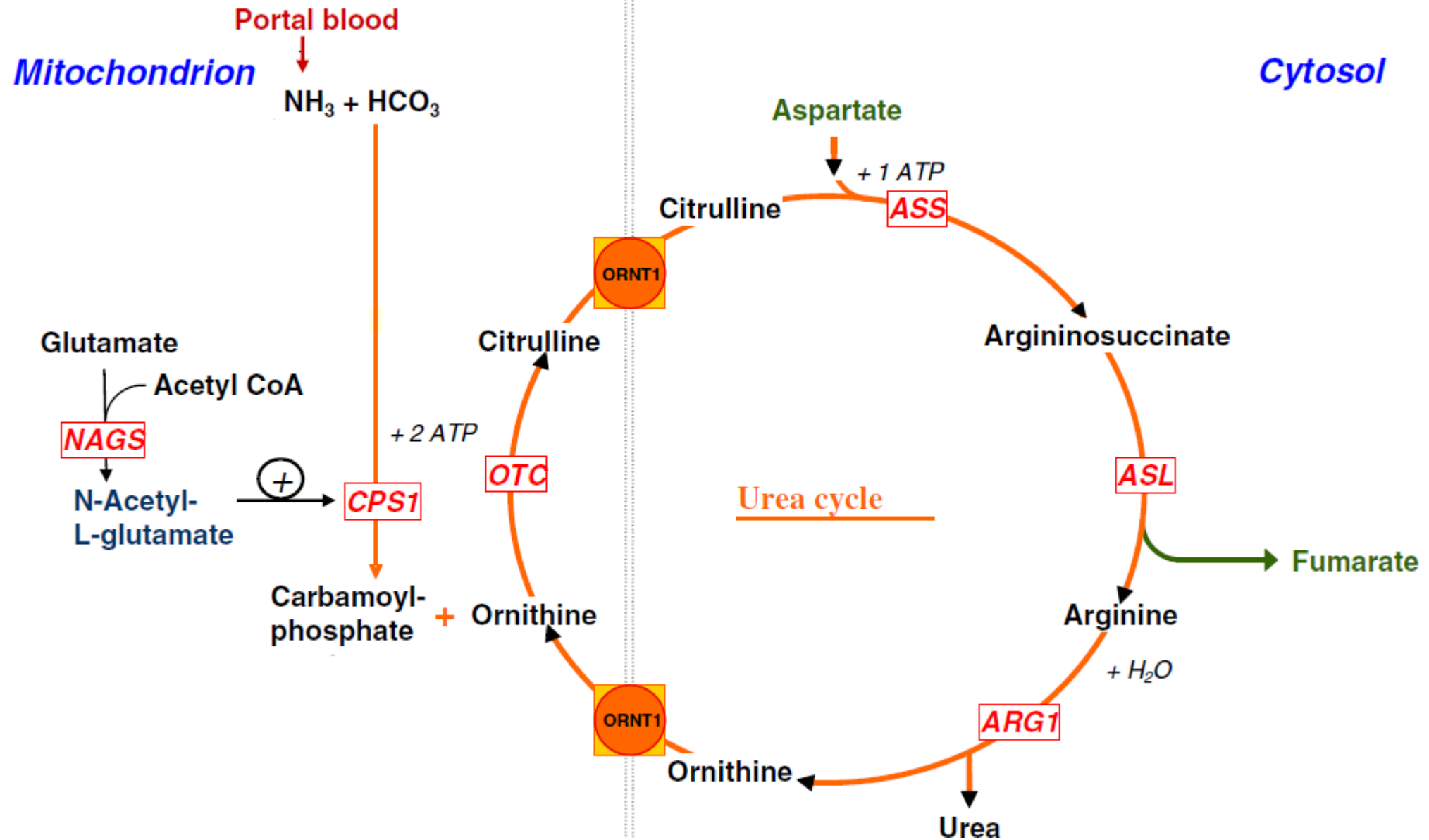
Introduction

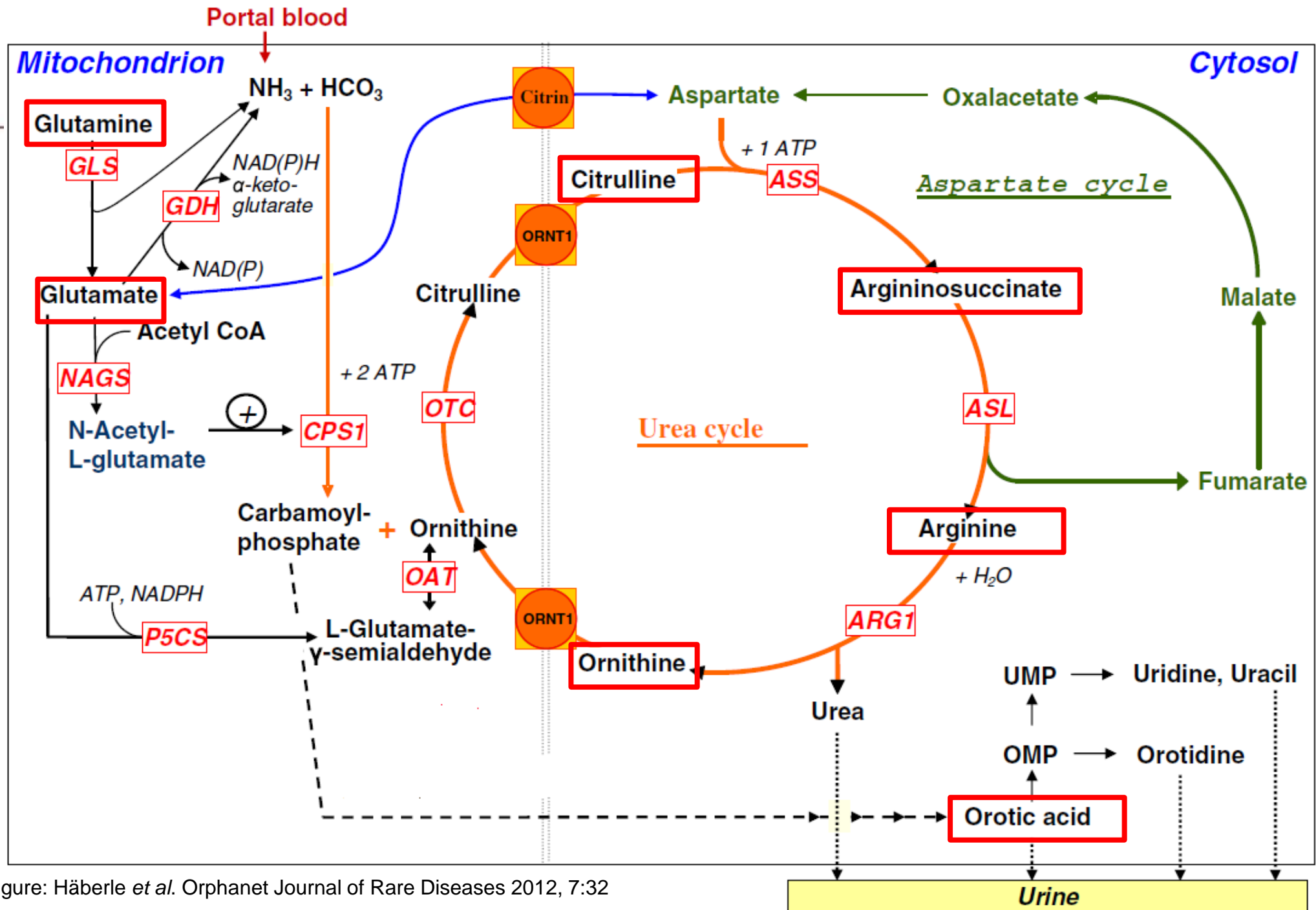
- **Hyperammonemia: clinical condition associated with \uparrow ammonia levels \rightarrow neurological complications**
- **Plasma ammonia exceeds:**
 - 100 $\mu\text{mol/L}$ in newborns
 - 50 $\mu\text{mol/L}$ in older individuals
 - $> 100 \mu\text{mol/L}$ SUSPECT AN IEM
- **Primary \rightarrow enzyme/transporter deficiencies in the urea cycle**
- **Secondary / acquired \rightarrow conditions affecting urea cycle indirectly**
 - Organic acidemia, Fatty acid oxidation disorders
 - Drug induced and hepatic illness/dysfunction not related to an IEM

The lost clue for differential diagnosis of an IEM

Clinical presentation

Age group	Gastro-intestinal	Neurological	Psychiatric
Neonates	+++ Poor feeding, gastroenteritis	+ Coma/death	-
Infants to children	++ Feeding problem → poor weight gain	+++ Seizures, intellectual impairment, headaches/migraines	+ Irritability, hyperactivity, sleep disturbances
Adolescents to adults	+ Protein avoidance	+ Intermittent ataxia, intellectual impairment, headache/migraines	+++ Irritability, hyperactivity, manic episodes, psychosis, sleep disturbances

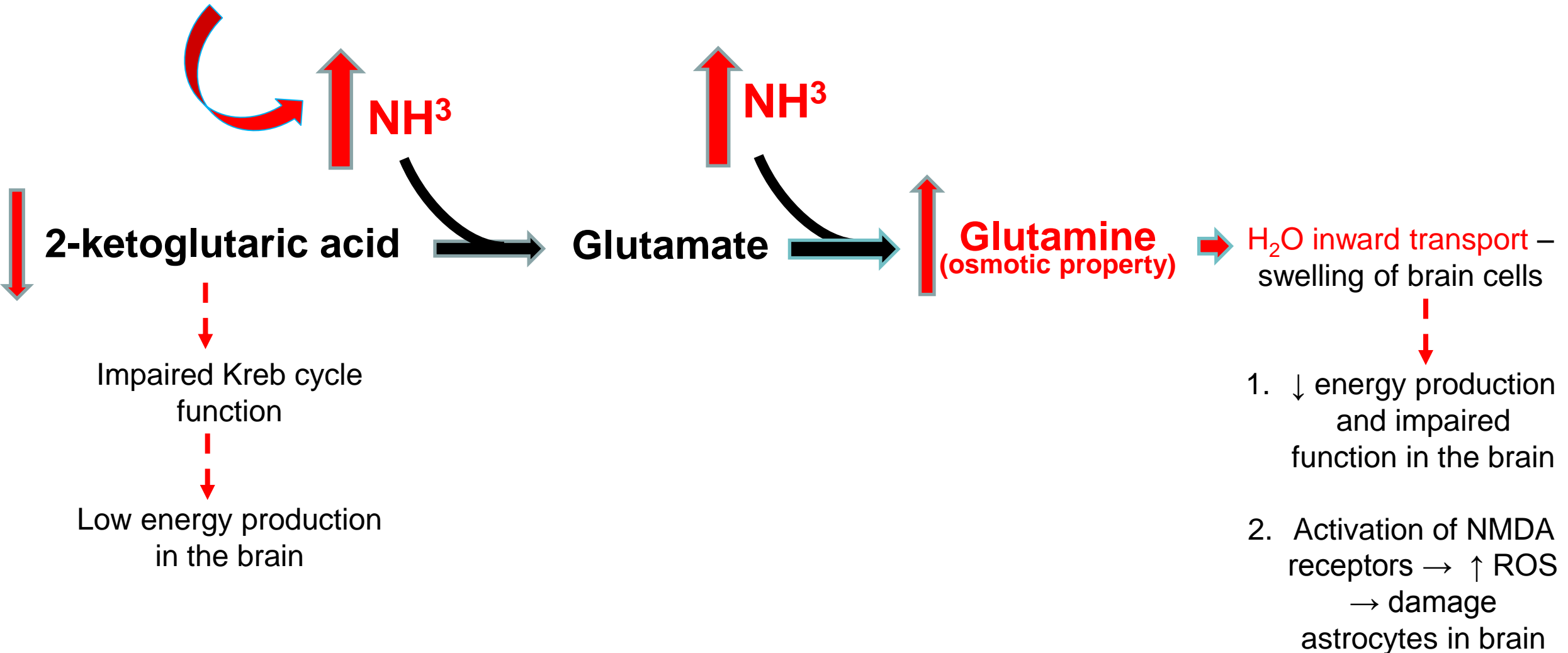




Modified figure: Häberle *et al.* Orphanet Journal of Rare Diseases 2012, 7:32

Mechanism of ammonia toxicity in the brain

X Urea cycle function



Common IEMS associated with Hyperammonemia

Organic acidemias

- Short chain organic acids has a direct influence on NAGS and CPS1 activity
- NH^3 : \uparrow - $\uparrow\uparrow\uparrow$ (Dercksen et al 2014).

Hyperinsulinemia-Hyperammonemia (HIH) syndrome

NH^3 : \uparrow - $\uparrow\uparrow\uparrow$ with hypoglycaemia

Urea cycle disorders (UCDs)

- Defective conversion of NH^3 to Urea
 - Enzyme disorder NH^3 : \uparrow - $\uparrow\uparrow\uparrow$
- Transporter and secondary enzyme defect NH^3 : n- $\uparrow\uparrow$

Fatty acid oxidation and carnitine transporter disorders

- mitochondrial and hepatic dysfunction
 - NH^3 : n- $\uparrow\uparrow$

IEMS resulting in secondary hepatic dysfunction:

- NH^3 : n- \uparrow
- Tyrosinemia, galactosemia, α_1 -antitrypsin deficiency

Non-IEMS resulting in hyperammonemia

Illness and infection

Increased Ammonia Production	Decreased Ammonia Elimination
Infection	Liver failure
Urease producing bacteria (Proteus, Klebsiella)	Fulminant hepatic failure
Herpes infection	Trans-hepatic, intrajugular
Protein load and increased catabolism	Shunt
Severe exercise	Portosystemic shunt (TIPSS)
Seizures	
Trauma or burns	
Steroid administration	
Chemotherapy	
Starvation	
Gastric bypass	
GI hemorrhage	
Increased renal ammonia production	
Increased splanchnic ammonia production	
Increased peripheral catabolism due to deficiency of essential amino acids	
TPN	
Other	
Cancers (multiple myeloma)	

*TIPSS = transjugular intrahepatic portosystemic shunt.

Medication

Drugs Associated With Fulminant Hepatic Failure	Drugs Associated With UCDs
Acetaminophen	Glycine
Lipid-lowering agents: atorvastatin	Salicylates
Antiinflammatories: ibuprofen, celecoxib, diclofenac	Valproate
Anesthetics: halothane	Carbamazepine
Antibiotics: amoxicillin, amoxicillin clavulonate, flucloxacillin, telithromycin, moxifloxacin, levofloxacin, trovafloxacin, minocycline, sulfamethoxazole, trimethoprim	Sulfadiazine
HIV medications: indinavir, nevirapine	Pyrimethamine
Antifungals: fluconazole, terbinafine	TPN
Anti-tuberculous medications: isoniazid, rifampin, rifabutin, pyrizinamide	
Antiparasitic: dapsone	
Anti-epileptics: carbamazepine, valproate, phenytoin, phenobarbital	
Anti-depressants: nefazadone, sertraline, duloxetine, bupropion	
Other psychoactive: lamotrigine, donepezil, disulfiram	
Illegal drugs: MDMA (ecstasy)	

*MDMA = 3,4 methylenedioxymethamphetamine.

Initial establishments of hyperammonemia

- **Should be included if IEM is suspected**
 - Challenges: Instability issues → Delayed analysis result in falsely elevated ammonia value
 - Collection without tourniquets
 - Sample should be put and transported on ice immediately after collection
 - Analyze immediately (no more than 15-30 min after collection)
- **Point-of-care device is available**
 - Small/mobile clinics and home support for families with IEMS

THE POCKETCHEM™ BA

EMERGENCY BLOOD AMMONIA MEASUREMENT



- Whole blood measurement
- Small sample volume
- Battery powered
- Easy to maintain
- Temperature compensation
- Data management function
- Lightweight and compact design
- Uses exclusive reagent strips without any pre-treatment

Routine Chemistry

Occurrence/ Parameter	UCD #	OA	FAO disorder *	HIH syndrome
Acidosis	-/+	+ - +++	-/+	-
Ketonurie	-	+ - ++	-	-
Hypoglycaemia	-	+/-	-	+
Lactate	-	+ - ++	+	-
Liver function (AST/ALT)	Mostly +	-	-/+	-
Creatine Kinase	-	-	+	-

*During fasting/metabolic crisis

Urea cycle transporter disorders may have normal routine chemistry

Note: Additional conditions resulting in hyperammonemia may include: mitochondrial disorder, pyruvate carboxylase deficiency, ornithine amino transferase deficiency, LPI, liver related IEMs


Specialized metabolic testing

Metabolic testing	UCD	OA	FAO disorders	HHH syndrome
Amino acids (Specifically glutamine and citrulline)	√√ (B and U)			
Organic acids		√√ (U)	√ (U)	
Orotic acid	√ (U)			
Free carnitine and Acylcarnitines		√ (U)	√√ (B and U)	
DNA	√			√

- **Additional tests to excluded galactosemia, tyrosinemia, ornithine amino transferase deficiency, and α_1 -antitrypsin deficiency is also recommended**
- **NB: Exclude non-IEM hyperammonia**

Enzyme and DNA testing

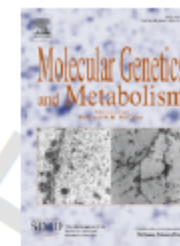
- Unexplained hyperammonemia without significant abnormality in metabolite profile may require Enzyme and DNA testing
- Example NAGS and CPS1 deficiency



Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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A novel UPLC-MS/MS based method to determine the activity of *N*-acetylglutamate synthase in liver tissue

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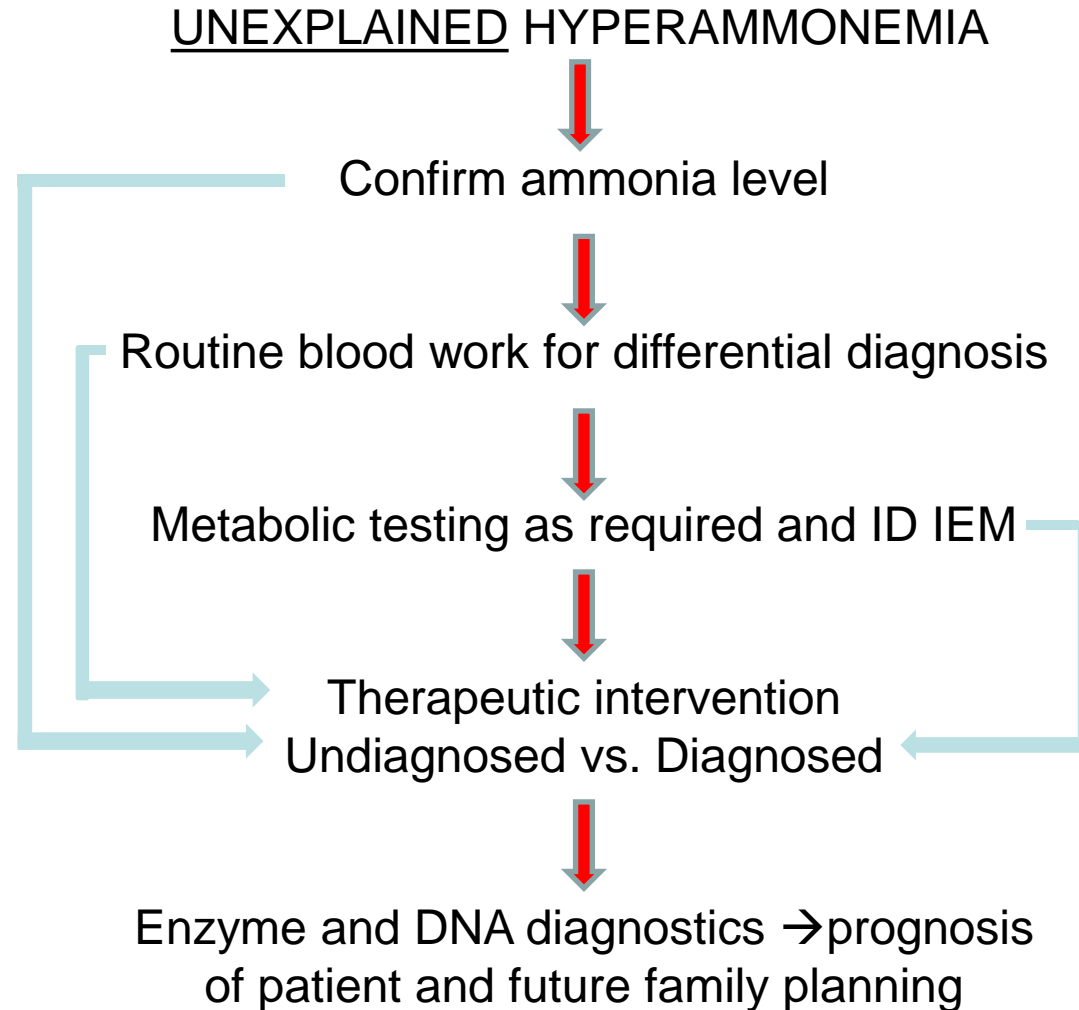
^c Children's National Medical Center, The George Washington University, Washington, DC, USA

Therapeutic intervention

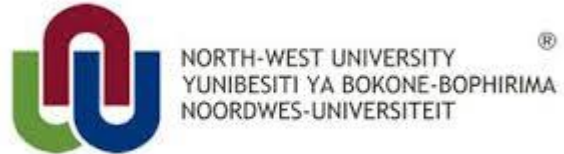
Ammonia level (μmol/l)	Undiagnosed	Diagnosed*
Above upper limit of normal	Limit/stop protein intake	Same as for undiagnosed
	IV glucose, avoid fasting	
>100 but < 250 (neonates) >150 but < 250 (older patients)	Same as above	Same as above Start supplementation and nitrogen scavengers according to the protocol of each disorder <ul style="list-style-type: none"> • UCD disorders: Carbaglu®, L-Citrulline, L-Arginine • OA disorder: L-Carnitine and Glycine for IVA • FAO disorders: +/- MCT feeding/L-Carnitine <ul style="list-style-type: none"> • HIH: Diazoxide
	Nitrogen scavengers (sodium benzoate and phenylbutyrate)	
	Intermediate/detoxifier and cofactor administration: (L-arginine, L-carnitine, biotin and Vit B12)	
250-500	Same as above	Same as for undiagnosed
	Prepare for dialysis	
	Begin dialysis, if no rapid drop of ammonia within 3–6 hours	
500	Same as above	Same as for undiagnosed
	Dialysis	

* Treatment plan should be revised according to specific diagnosis and adjusted according to acute vs. chronic presentation

SUMMARY



Thank you



Prof Chris Vorster and the Centre for Human metabolomics
(<http://natural-sciences.nwu.ac.za/human-metabolomics> and www.pliem.co.za)



Prof Ronald Wanders and Lab GMZ at the Amsterdam medical center, University of Amsterdam, the Netherlands