Overview on treatment of metabolic disorders

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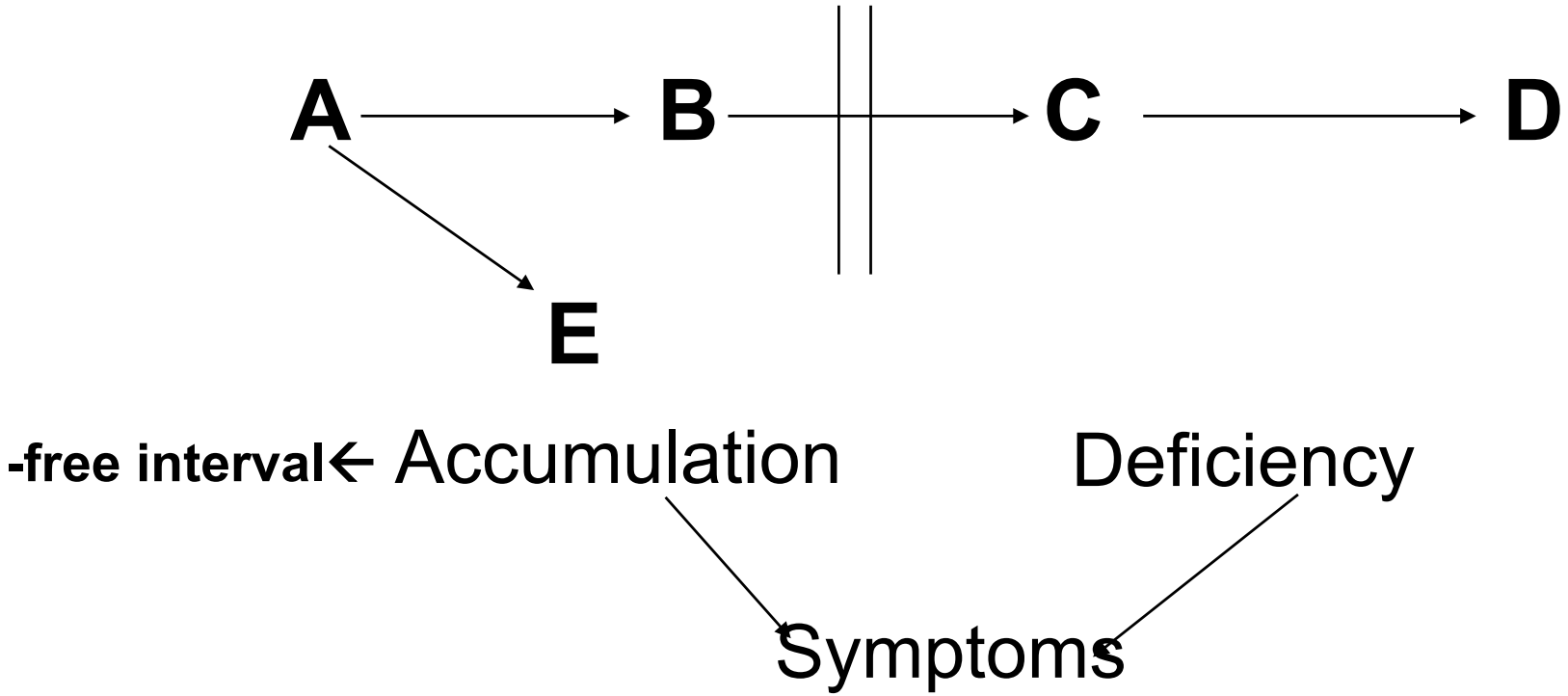
Inborn Errors of



outline

- Treatment in diseases with intoxication or energy deficiency
  - acute management
  - chronic management: diet decreasing precursors , cofactors, substrate supplementation
- Treatment in complex molecules
  - HSCT, ERT, Chaperones, substrate inhibition, gene therapy

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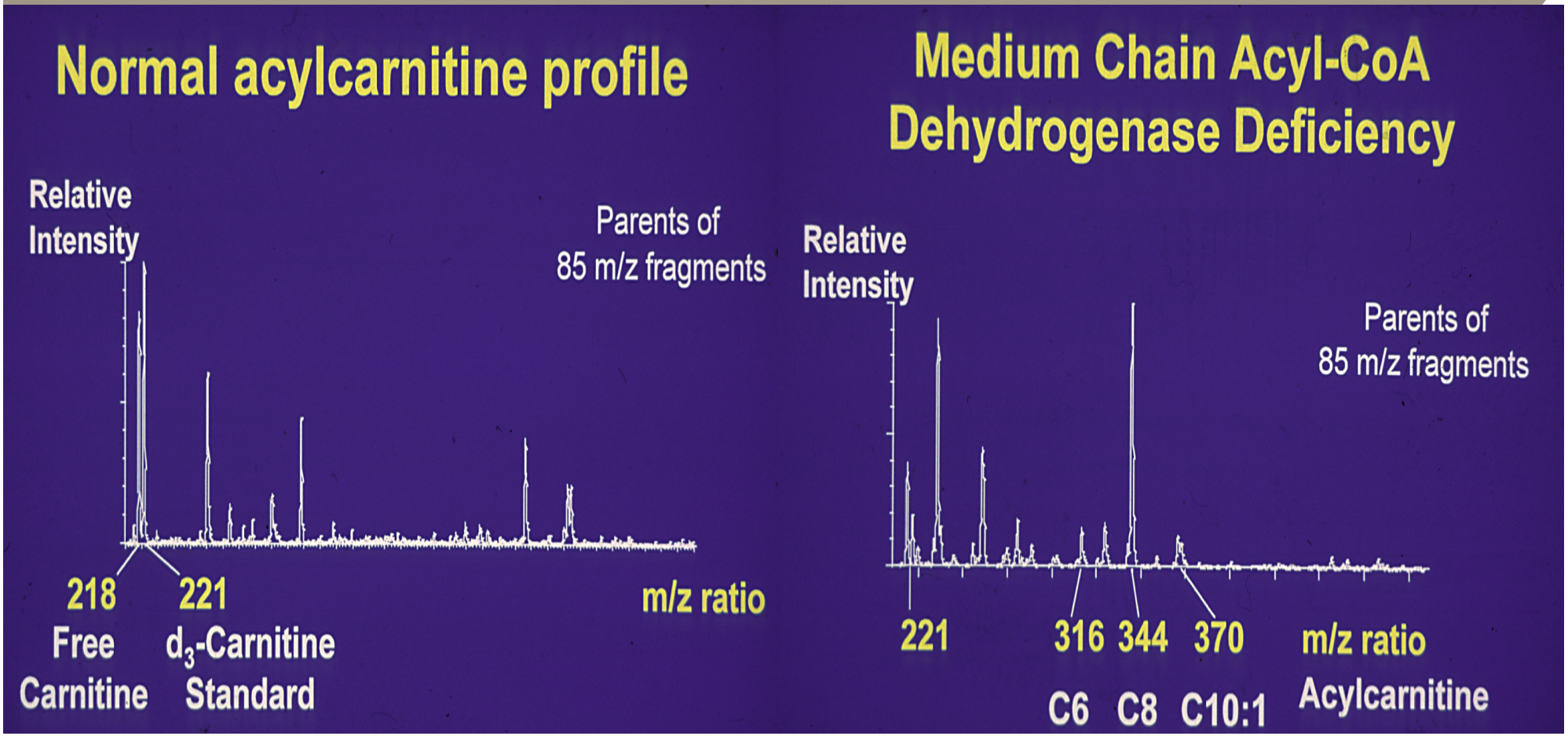
Neonatal Screeningtests

aminoacids	**FAO / OA disorders**	**other**
Fenylalanine	MADD	TSH
Tyrosine	SCAD	17-hydroxyprogesteron
Leucine	MCAD	biotinidase
Methionine	LCAD	
Ornithine	LCHAD / MTP	
Citrulline	VLCAD	
Glycine	CPT II	
Alanine	CPT I	
	HMG	
	GA I	
	PA	
	MMA	
	IVA	



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Neonatal screening tests

- Early diet treatment in PKU
  → Low protein, supplements of aminoacids, Kuvan (BH4)
- Early diagnosis MCAD preventive measures
- Early diagnosis urea cycle disorder
  → Prevent damage and start adequate diet
  → Carbaglu in NAGS deficiency
- Necessary vitamins vitB12 in MMA
- **Goal:** start early treatment to prevent damage and prevent catabolism

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Fluid management acute lactic acidosis

J Inher Metab Dis
Katharina Danhauser et al; 2014

- Normocaloric feeding and adequate fluid supplementation orally or via gastric tube
- Early placement of central venous line for buffering and parenteral nutrition is required
- Avoid catabolism
- Infusion therapy with caution : high glucose supplementation might worsen lactic acidosis

Fluid management during metabolic crisis

- starting infusion at a moderate glucose rate 5–6 mg/kg/min
- monitor serum glucose and lactate levels
- if tolerated well, glucose rate might be further increased up to 7–8 mg/kg/min
- serum glucose levels should not exceed

  100 -120 mg/dl (5.6–6.7 mmol/L)

Fluid management during metabolic crisis

- additional insulin to lower glucose and increase cellular glucose uptake
- Caution might worsen intracellular glucose utilization problem and aggravate acidosis
- monitoring of balance between glucose and lactate levels becomes unreliable
- if glucose infusion is not tolerated well, increased administration of fat (2–3 g/kg/day) to achieve adequate calories

Buffering

- rapid correction of blood pH
  - → may worsen cerebral acidosis due to abrupt suppression of hyperventilation stimuli
  - → increased blood pCO_2, which crosses the blood brain barrier faster than HCO_3^-
  - → brain edema may develop

Buffering

- Sodium bicarbonate most commonly used
  After injection, sodium bicarbonate
  -> Na^+ and $HCO3^-$ -> CO2 and water
- Acidosis can be subsequently reduced by exhalation of CO2
- several side effects
  → hypernatremia, volume overload, exacerbation intracellular acidosis, hyperosmolality, development of cerebral edema, hypokalemia, hypocalcemia, and reduced cardiac contractility

Buffering calculation

HCO_3^-(mmol)=HCO_3^- (target value) - HCO_3^- (initial value) x BW (kg) x 0.3

or

HCO_3^-(mmol)= BE x 0.3 x BW (kg)

0.3 = derived 30%; neonatal 0.4 preterm 0.5

- Half of calculated sodium bicarbonate infused over 1-2hr
- Remaining at slower rate

Specific treatment in lactic acidosis

- thiamine supplementation
  - → effective in thiamine responsive PDHC deficiency or thiamine pyrophosphokinase deficiency 15–30 mg/kg/day
- thiamine (and biotin) may be life saving in unclear disease conditions
  - → thiamine deficiency
  - → thiamine metabolism disorders (biotin-thiamine-responsive basal ganglia disease)

Specific treatment options

- riboflavin
  - → patients with mitochondrial complex I deficiency caused by ACAD9 mutations
  - → 10 mg/kg/day up to max 300 mg/day
  - → Fatty oxidation defects
- Other therapeutic possibilities
  - → cofactor
  - → electron donor and acceptor properties

Specific treatment options

- Coenzyme Q10
  - → Suspected Coenzyme Q10 deficiency disorders
  - → 5–20 mg/kg/day up to max 1 g/day
- Ketogenic diet
  - → PDHc deficiency
  - → neuroprotective, antiepileptic and mitochondriotropic effect
- Phenylbutyrate therapy
  - → Future option PDHC deficiency

Dichloroacetate

- PDH deficiency
- PDH complex remains in active state

- 25mg/kg/day in 2 doses oral or IV
- Longterm treatment not recommended

RK, 7 day old ♀

- Born at term, birth weight of 3.070kg uncomplicated
- Formula fed from birth
- Family history:
  → consanguineous parents
  → brother of 5 years: healthy

Admitted to peripheral hospital

- 1 day history of vomiting and poor feeding

- Managed as a dehydration
  → ORS via NG tube
  → Next morning formula feeds reintroduced

- Next day
  → Transient episode of SVT -> resolution after adenosine x 2
  → Transfer to PICU, UZ Brussel

Admission to PICU

- Clinically

  → Lethargic, poor suck, incomplete Moro

  → Stable cardiovascular system – no SVT

  → No hepatomegaly

Investigations

- Septic screen (on blood, urine, CSF) – negative
- Cardiac work up ECG and echo – normal
- Metabolic screen (blood, urine, CSF)
  - → Normal glycemia, lactate, no ketones in urine
  - → Respiratory alkalosis : pH 7,48, pCO2 19mmHg, HCO3 14 mmol/l, BE -6,6mmol/l
  - → Normal serum acylcarnitines
  - → Hyperammonemia 290 µmol/l
    - Blood amino acids: high glutamine (1004 µmol/l) with normal citrulline
    - Urine organic acids: orotic acid normal

Question 1:

- What could be the diagnosis?

1. OCT
2. Citrullinemia
3. NAGS
4. MCAD

Question 1:

- What could be the diagnosis?
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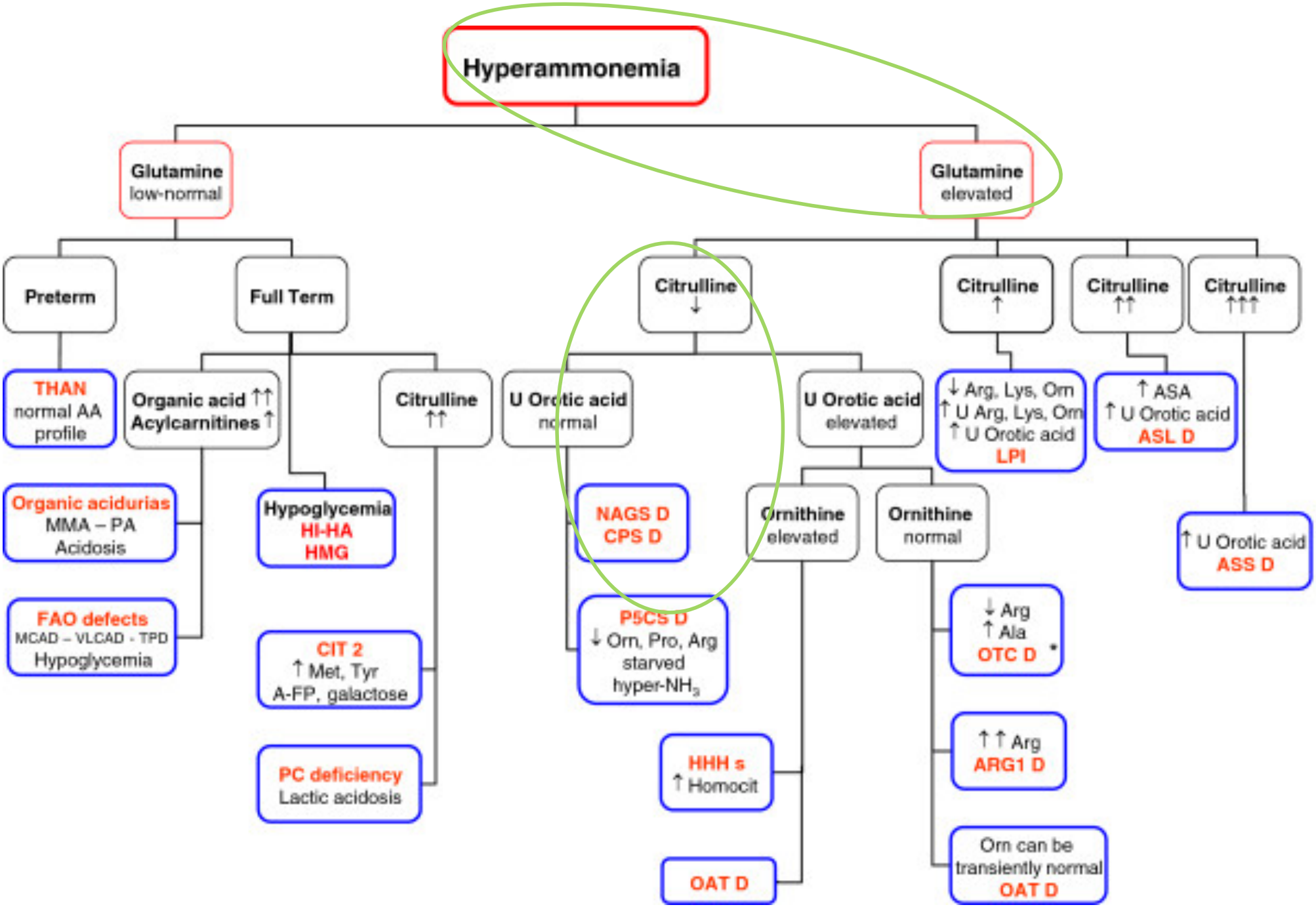
  2. Citrullinemia
  3. NAGS
  4. MCAD



J Häberle et al. *Suggested guidelines for the diagnosis and management of urea cycle disorders*, Orphanet journal of rare diseases 2012;7:32

Treatment options?

1. Stop all protein intake
2. Reverse of catabolism and optimization of caloric intake:
   - Glucose 10% -> 20% solution (110kcal/kg/d)
3. Promote nitrogen excretion:
   - Using ammonia scavengers: sodium benzoate: 250mg/kg/d
4. Enhancing availability of urea cycle enzymes: L-arginine 350mg/kg/d
5. Start N-carbamyl glutamate 100mg/kg/d
6. All

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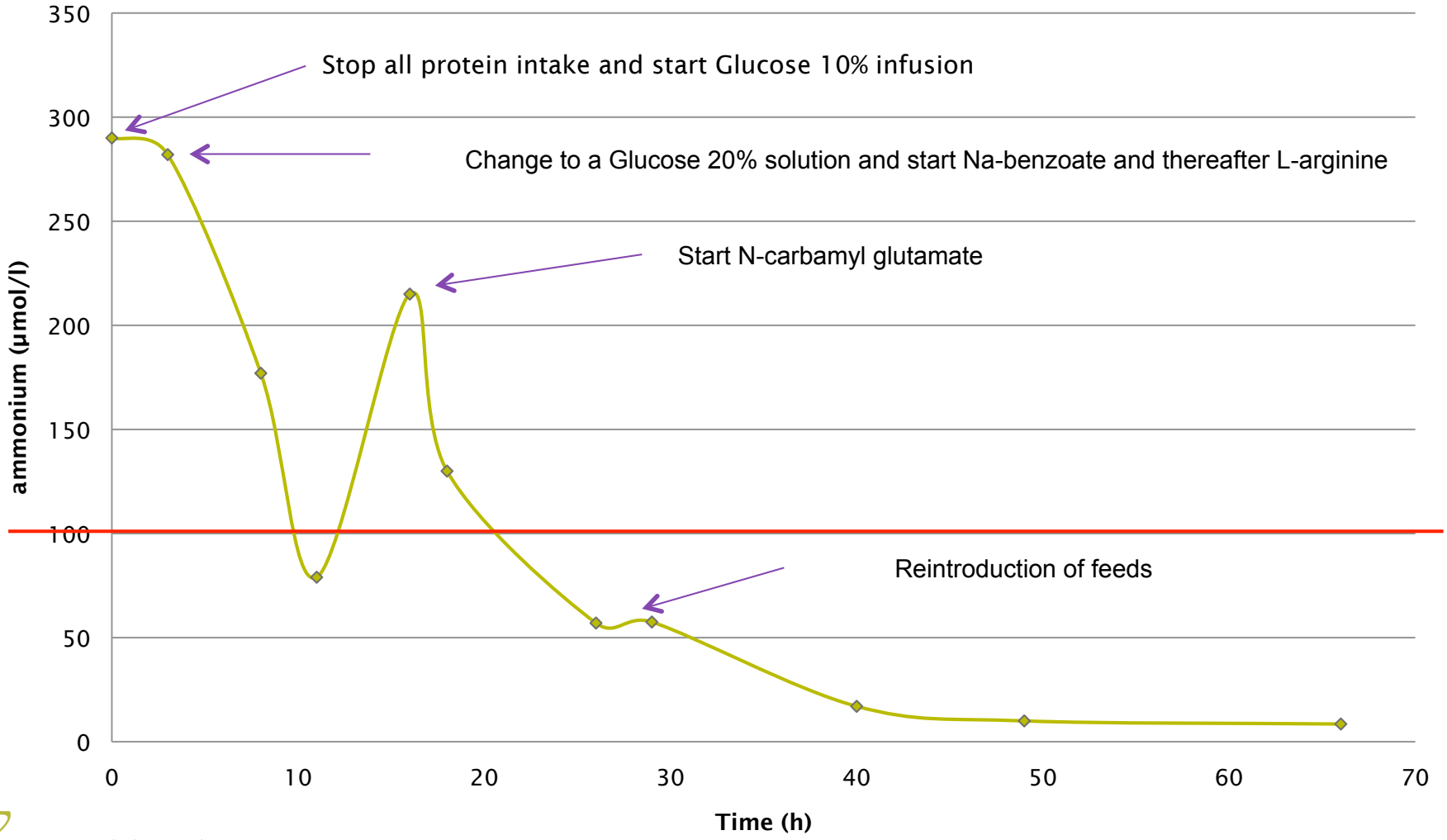
Evolution of NH3



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Further work up

- EEG 48h after admission: normal

- Genetic analysis NAGS gene (J. Häberle, Zurich) :
  - → homozygous mutation c. 1450T>C (p.W484R) in exon 6 of NAGS gene
  - → Carrier state in both parents

→ **NAGS deficiency**

NAGS deficiency

- NAGS synthezises NAG → activates CPS 1 of the urea cycle (= the rate limiting enzyme)

- NAGS Deficiency = high block of urea cycle
  → i.e. high glutamine and low citrulline

- Diagnosis:
  → differential diagnosis using AA and OA
  → further testing for exact diagnosis:
    - Liver biopsy for enzymatic essay (invasive)
    - Genetic analysis for detection of mutation

Hyperammonemia

- Prompt detoxification if NH3 > 500mM
- Stop protein intake and total parenteral feeding
- Remove ammonia by adding Na-benzoate
- Add arginine hydrochloride 360mg/kg
- Carnitine IV unless FAO is suspected
- Haemofiltration
- Consider Carba-glu 100mg/kg /day for NAGS and CPS1
- Intralipid after exclusion FAO

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Metabolic and epilepsy

- Ony small part of epilepsy 1- 2%
- Specific therapy
- Genetic counseling
- multiple seizures unexplained status epilepticus
- ---> think also metabolic

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Deficiencies

- **ENERGY SUPPLY**
  - Glut 1 deficiency
  - Glycolysis, Krebs cycle, resp chain; POLG
  - Creatine deficiencies (GAMT, AGAT, CRTR)
- **ANABOLIC SUBSTRATE**
  - Serine biosynthesis defects
- **COFACTORS**
  - Pyridoxine responsive seizures, pyridoxal phosphate responsive seizures, folinic acid responsive seizures, biotinidase
- **NEUROTRANSMITTERS**
  - GABA transaminase, BH4 synthesis defects, L-AADC

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Accumulation

- **NEUROTOXIC METABOLITES**
  - GAMT deficiency; L2OH glutaric aciduria; GA1
  - Adenylosuccinate lyase
  - Non ketotic hyperglycinemia
- **COMPLEX MOLECULES**
  - Neuronal ceroid lipofuscinosis,
  - Niemann Pick type C
  - Tay Sachs, sialidosis I

Surtees, Wolf 2007

Complex mechanism

- **MIGRATIONAL DEFECTS AND CEREBRAL DYSPLASIAS**

- Peroxisomal biogenesis (Zellweger)
- Glutaric aciduria 2
- Molybdenum cofactor deficiency; sulphite oxidase deficiency
- CDG syndromes
- Pyruvate dehydrogenase deficiency

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Neonatal convulsions
pyridoxine responsive convulsies

- Often generalised tonic seizures
- Recurrent partial motor seizures
- Myoclonus
- Mixed seizure pattern
- Unilateral status epilepticus
- Triggered by hyperexcitation and crying
- Responsive to pyridoxine IV
- Caution apnea!!!

Pyridoxine dependent seizures

- Heterogenous clinical picture
- Gastrointestinal symptoms emesis and abdominal distension
- Sleeplessness
- Hyperalertness, irritability
- Facial grimacing and abnormal eye movements

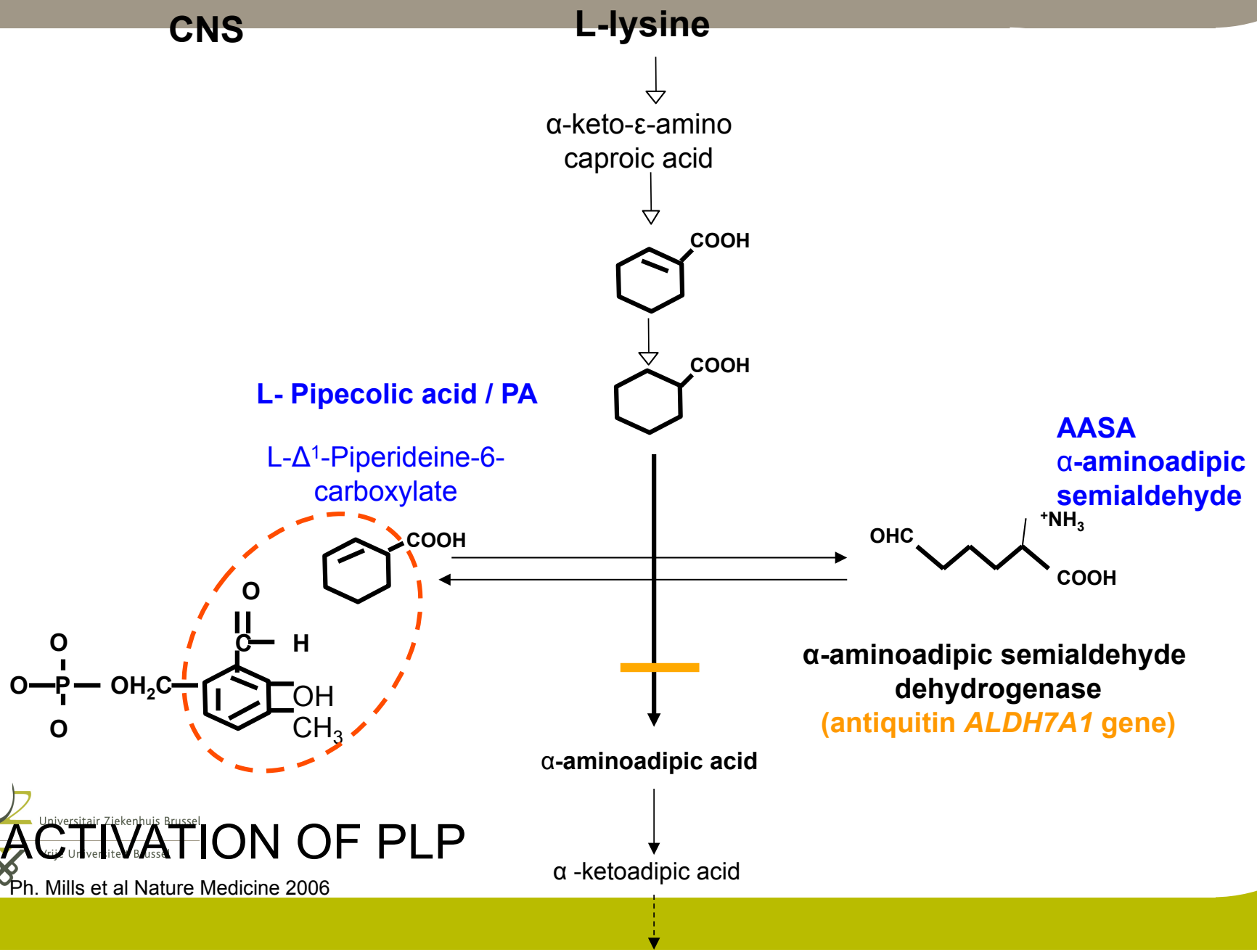
Clinical phenotypes 3 groups

- Complete seizure control with pyridoxine and normal development
- Complete seizure controle with pyridoxine but with developmental delay
- Persistent seizures and developmental delay despite pyridoxine

Pyridoxine dependent epilepsy

- Antiquitin ALDH7A1 gene aminodipic semialdehyde dehydrogenase; degradation pathway of lysine
- Inactivation of cofactor activity (piperideine-6-carboxylate condense with pyridoxal phosphate)
- Results in accumulation of α-aminoadipic semialdehyde (α-AASA)
- α-AASA can be found in urine

ENZYME DEFECT AND BIOMARKERS IN PDE



INACTIVATION OF PLP

Ph. Mills et al Nature Medicine 2006

Treatment of pyridoxine-dependent epilepsy

- Acute pyridoxine 100mgIV
- Pyridoxine Oral 15-30mg/kg in 3 doses; up to 200mg/day in neonates; é00-300mg in adults !!peripherla neuropathy
- Lysine restricted diet
- Arginine 150mg/kg/day not proven

Original article

Novel therapy for pyridoxine dependent epilepsy due to *ALDH7A1* genetic defect: L-arginine supplementation alternative to lysine-restricted diet

Saadet Mercimek-Mahmutoglu [a,b,*], *Dawn Cordeiro* [a], *Vivian Cruz* [a], *Keith Hyland* [c], *Eduard A. Struys* [d], *Lianna Kyriakopoulou* [e], *Eva Mamak* [f]

European Journal of Paediatric Neurology (2014),

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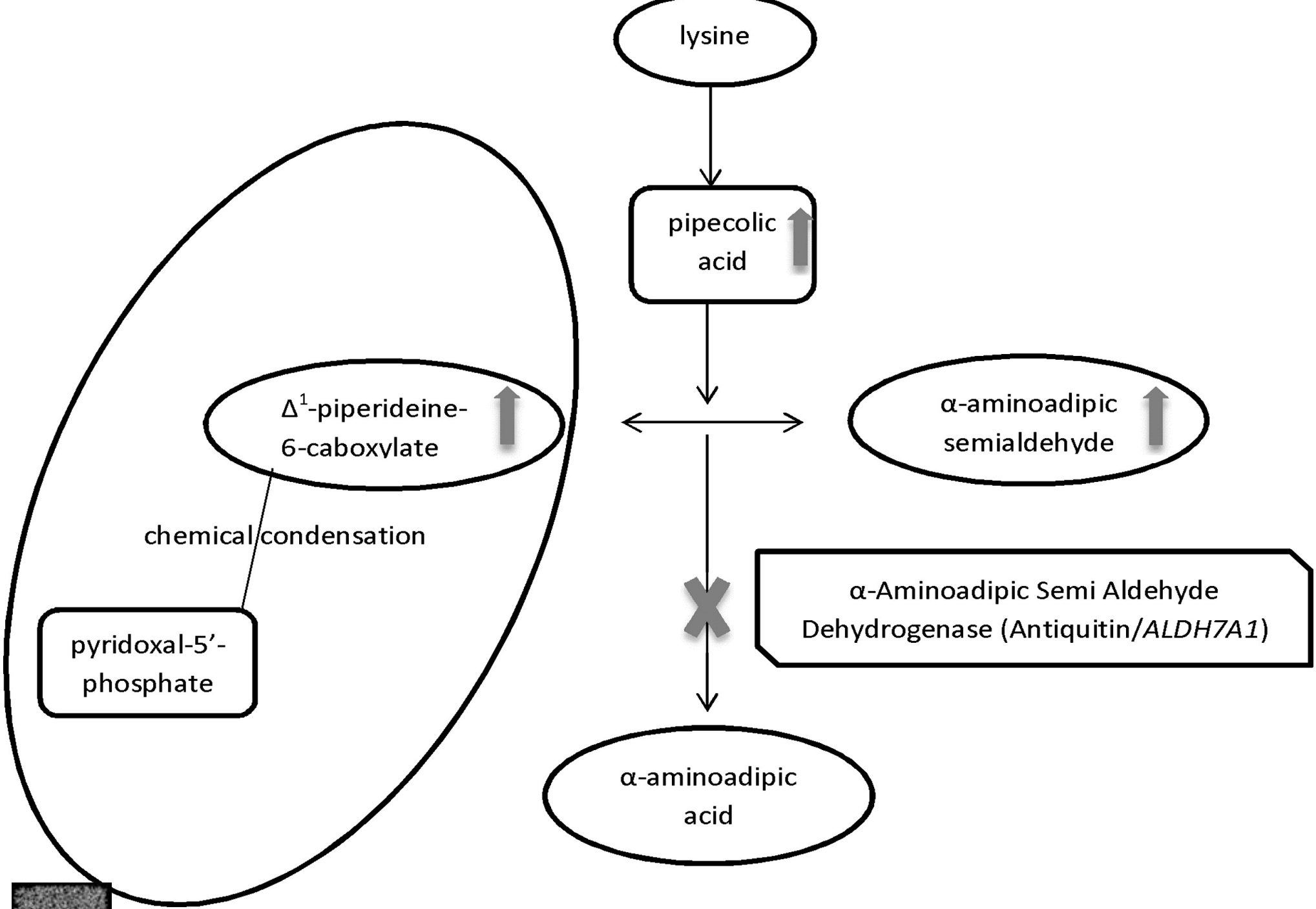

Molecular Genetics and Metabolism 2012 107, 335-344DOI: (10.1016/j.ymgme.2012.09.006)

Treatment diet

- Lysine restriction : result in reduction of AASA /P6C accumulation and might lead to improvement of neurodevelopmental outcome

- L-arginine : cerebral lysine and oxidation can be modelated by arginine, by competition with lysine for transport at blood-brain barrier →reducing excess of lysine influx into the brain

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Treatable neonatal seizures

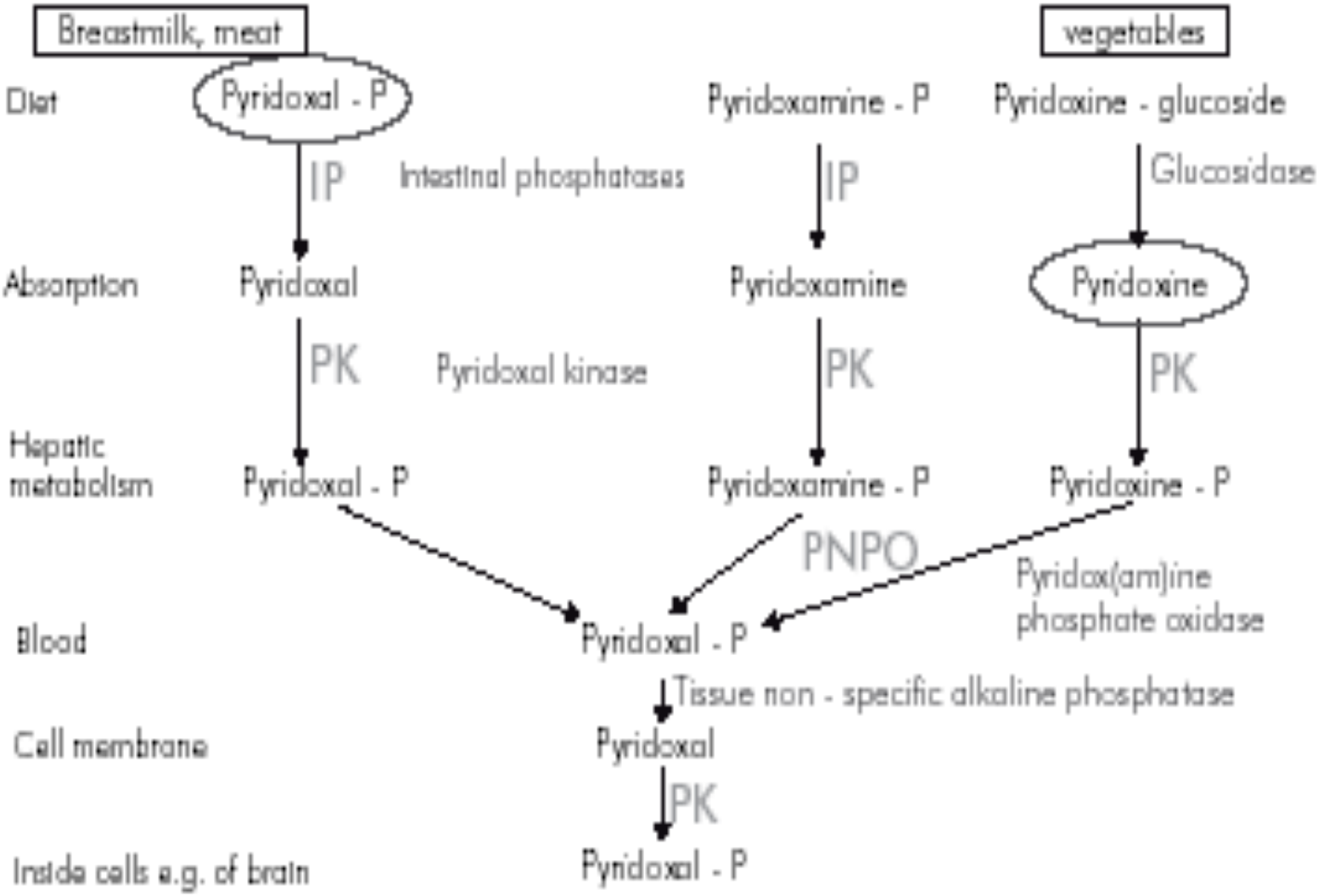
- Pyridoxine dependent convulsions
  - → alpha-aminoadipic semialdehyde (ASAA) in urine
  - → Deficiency alpha-amino adipic semialdehyde (AASA) dehydrogenase (antiquitin) in the cerebral lysine degradation pathway.
  - → Pipecolic acid (PA) and AASA are increased in urine, plasma, and CSV

- Pyridoxal phosphate responsive convulsions
  - → Low HVA and 5HIAA; high glycine and threonine in CSV
  - → Treatment with pyridoxal phosphate instead of pyridoxine
  - → Mutations in PNPO gen for pyridox(am)ine 5'-phosphate oxidase and in PROSC

PNPO

- premature birth; seizure onset day 1 in utero
- clonic, status, myoclonus, rotatory eye movements, hyperexcitability
- EEG severe burst suppression, myoclonic
- hypoglycemia, early acidosis, pancytopenia, coagulopathy; neurotranssmitter dysfunction L-AADC; raised glycine, threonine, taurine , low arginine
- PLP 30 to 50 mg/kg/day in 3-4 SD

Pyridoxal phosphate responsive convulsions



Mutations in PNPO gen for pyridox(am)ine 5'-phosphate oxidase

The American Journal of Human Genetics
99, 1325–1337, 2016

Proline synthetase co-transcribed homolog

Mutations in *PROSC* Disrupt Cellular Pyridoxal Phosphate Homeostasis and Cause Vitamin-B_6-Dependent Epilepsy

Niklas Darin,[1] Emma Reid,[2] Laurence Prunetti,[3] Lena Samuelsson,[4] Ralf A. Husain,[5] Matthew Wilson,[2] Basma El Yacoubi,[3,17] Emma Footitt,[6] W.K. Chong,[7] Louise C. Wilson,[8] Helen Prunty,[9] Simon Pope,[10] Simon Heales,[2,9,10] Karine Lascelles,[11] Mike Champion,[12] Evangeline Wassmer,[13] Pierangelo Veggiotti,[14,15] Valérie de Crécy-Lagard,[3] Philippa B. Mills,[2,16,*] and Peter T. Clayton[2,16,*]

Treatable neonates and infants

Neonates

- **Pyridoxine dependent seizures**
  - Diagnosis alpha-aminoadipic semialdehyde
  - antiquitin ALDH7A1
- **Pyridoxal phosphate responsive seizures**
  - Low HVA and 5HIAA; high glycine and threonine in CSF
- **Folinic responsive seizures** antiquitin ALDH7A1
- **Serine biosynthesis** Low CSF serine
- **CAD deficiency**

After neonatal period

- Biotinidase (usually later)
- Cerebral creatine deficiency high GAA, low creatine; MRs- spectroscopy
- Glut1 deficiency ketogenic diet

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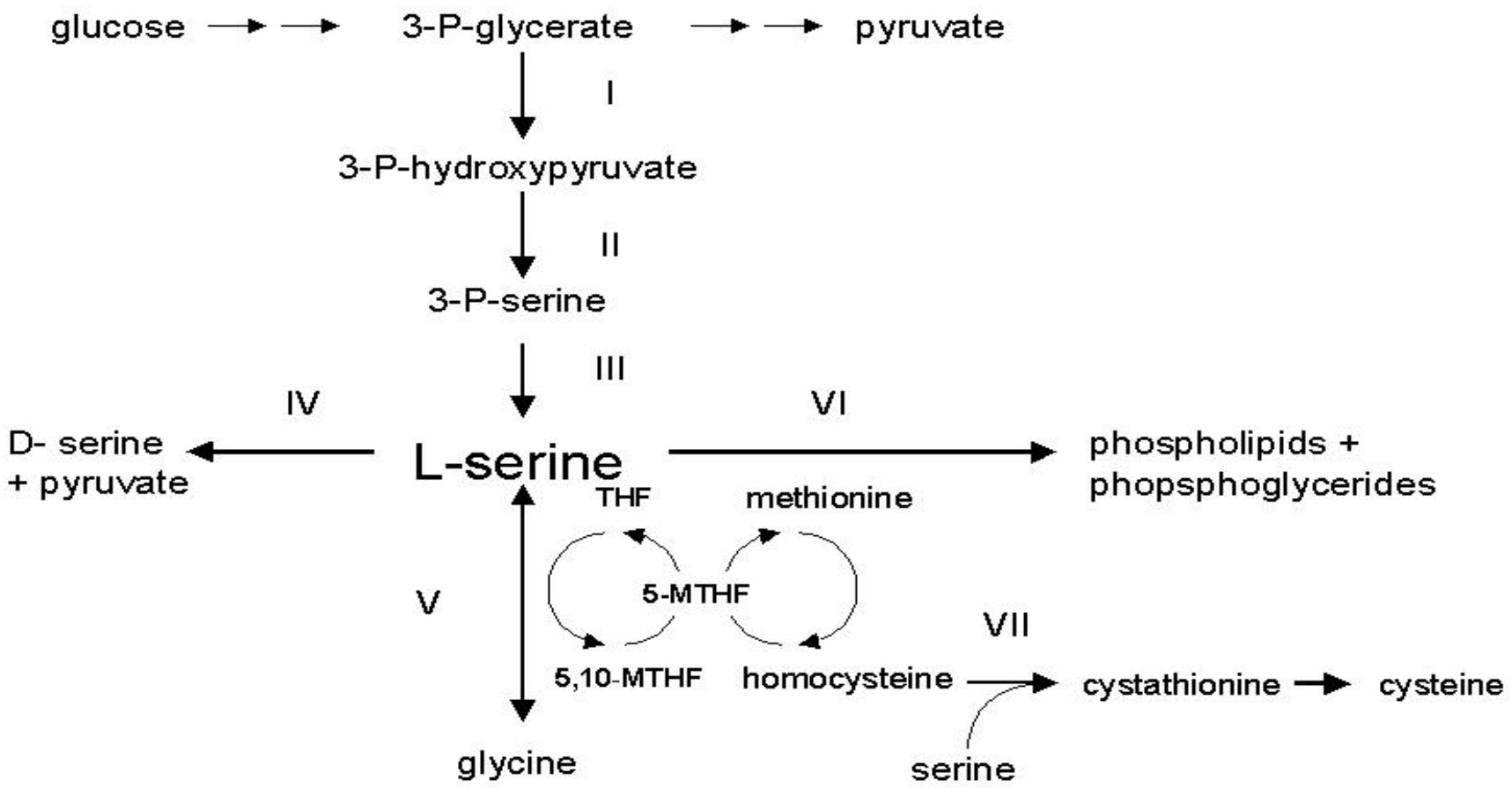
L-serine biosynthesis

Figure 1



Serine biosynthesis and substrate supplementaion

- low serine and glycine in CSF, while plasma serine normal
- Congenital microcephaly, epilepsy and profound psychomotor retardation

- 3-phosphoglycerate →hydroxypyruvate→P-serine→ serine
- Treatable with L-serine

3-phosphoglycerate dehydrogenase deficiency

- Infantile phenotype
- Juvenile phenotype

De Koning, 2011

3-PGDH infantile phenotype

Key clinical features:

- Microcephaly (congenital)
- Seizures
- Severe inteleectual disabilitu

Amino acid treatment

- Infantile phenotype
  - → Improved well-being
  - → Significant reduction in seizure frequency
  - → Biochemical correction of abnormalities
  - → In symptomatic patients there was no progress of development
  - → Only in a presymptomatic patient progression of development
- L-serine orally 500-700 mg/kg/day

BRAIN 2016

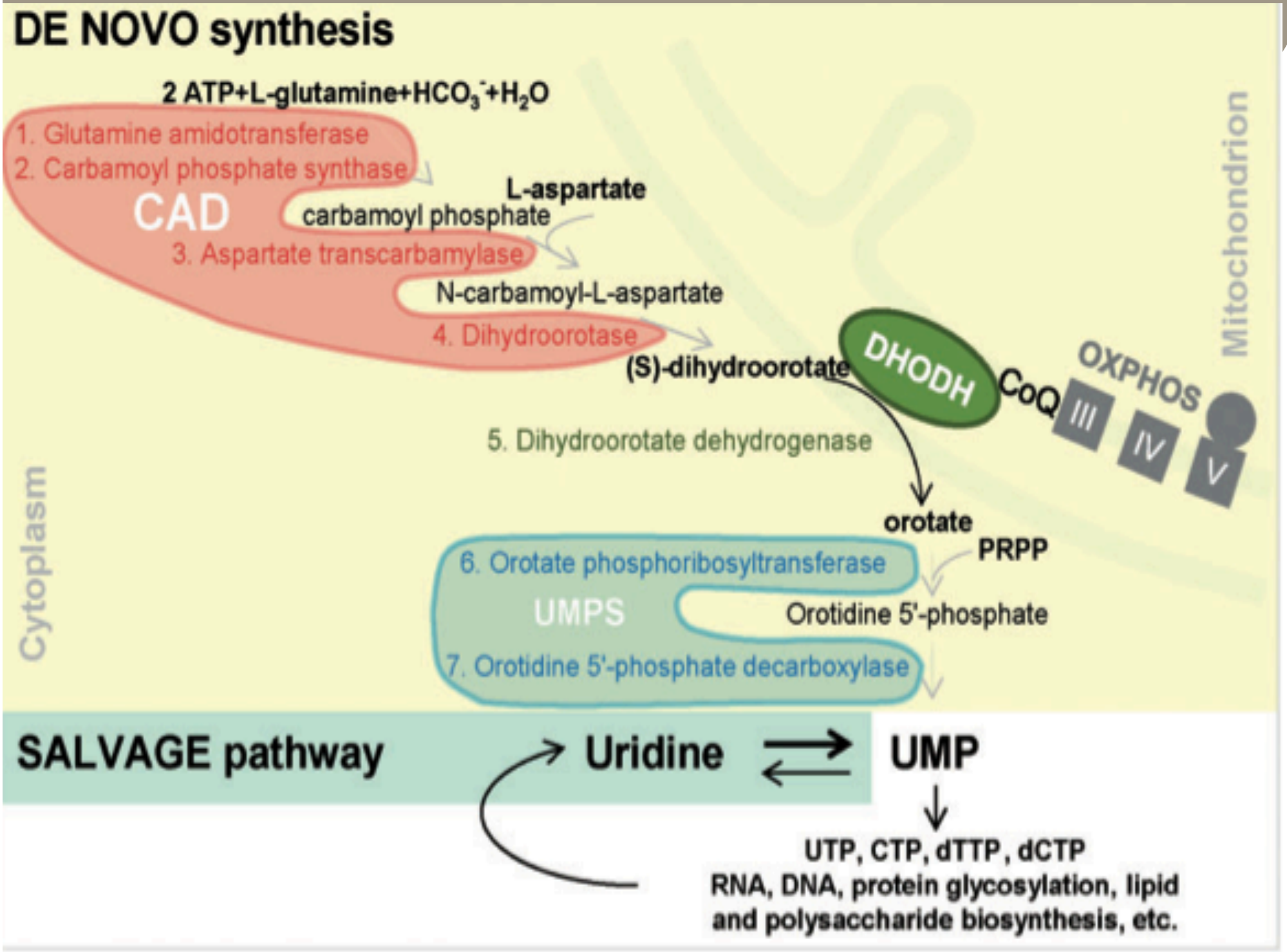
REPORT

CAD mutations and uridine-responsive epileptic encephalopathy

Johannes Koch,[1,*] Johannes A. Mayr,[1,*] Bader Alhaddad,[2] Christian Rauscher,[1] Jörgen Bierau,[3] Reka Kovacs-Nagy,[2] Karlien L. M. Coene,[4,5,6] Ingrid Bader,[1] Monika Holzhacker,[1] Holger Prokisch,[2,7] Hanka Venselaar,[5] Ron A. Wevers,[4] Felix Distelmaier,[8] Tilman Polster,[9] Steffen Leiz,[10] Cornelia Betzler,[11] Tim M. Strom,[2,7] Wolfgang Sperl,[1] Thomas Meitinger,[2,7,12] Saskia B. Wortmann[1,2,7,*] and Tobias B. Haack[2,7,†,*]

CAD

- multifunctional enzyme involved in de novo pyrimidine biosynthesis
- alternatively, pyrimidines can be recycled from uridine
- three families identified biallelic CAD mutations in four children with global developmental delay, epileptic encephalopathy, and anaemia with anisopoikilocytosis


DE NOVO synthesis
2 ATP+L-glutamine+HCO3-+H2O
1. Glutamine amidotransferase
2. Carbamoyl phosphate synthase
CAD
L-aspartate
carbamoyl phosphate
3. Aspartate transcarbamylase
N-carbamoyl-L-aspartate
4. Dihydroorotase
(S)-dihydroorotate
DHODH
CoQ
OXPHOS
III
IV
V
Mitochondrion
5. Dihydroorotate dehydrogenase
orotate
PRPP
6. Orotate phosphoribosyltransferase
UMPS
Orotidine 5'-phosphate
7. Orotidine 5'-phosphate decarboxylase
Cytoplasm
SALVAGE pathway
Uridine
UMP
UTP, CTP, dTTP, dCTP
RNA, DNA, protein glycosylation, lipid
and polysaccharide biosynthesis, etc.

CAD

- Two died aged 4 and 5 years after a neurodegenerative disease course.
- Supplementation of two surviving children with oral uridine led to immediate cessation of seizures in both
- A 4-year-old female, previously in a minimally conscious state, began to communicate and walk with assistance after 9 weeks of treatment.

CAD and uridine treatment

- blood smears normalized and anaemia resolved
- efficacy of uridine supplementation, rendering CAD deficiency a treatable neurometabolic disorder
- potential condition for future (genetic) newborn screening

metabolic epilepsy in infancy

- Hypoglycemia
- GLUT-1
- PDH deficiency
- creatine deficiency
- biotinidase
- amino acidopathies, organic acidurias
- CDG
- pyridoxine dependency
- infantile form of neuronal ceroid lipofuscinosis
- mitochondrial diseases

GLUT 1 (glucose transporter 1) deficiency

- Biological hallmark is the decrease of ratio CSF/blood glucose <0.4
- different phenotypes
  - → classical phenotype with early onset seizures microcephaly
  - → early onset absence seizures
  - → non-classical phenotype with mental retardation and movement disorder without epilepsy
  - → movement disorder
  - → milder phenotypes

GLUT 1

- **Seizures** all types

  severe myoclonic-atonic seizures

  generalised tonic-clonic

  absences

  nocturnal or early morning seizures

- **Genetics**

  autosomal dominant transmission

  mutations -> truncation of GLUT1 protein

  gene SLC2A1 1p35-p31.3

- CSF x study NT: N

  5MTHF : N

  Protein: 18 m/dL (15-40)

  Glucose: 34 mg/dL (40-61)

  Lactate: 10 mg/dL (10-20)

  AA CSF : N

  Glucose (P) : 110 mg/dL

  Ratio Glucose CSF/P : 0.31

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Treatment alternative fuel?

Ketogenic diet or low glycemic index diet

→ Controls seizures

→ Improves neurological function

Antiepileptic drugs

→ If poor seizure control / poor tolerance to diet

→ Carbamazepine or Phenytoin

Avoidance of inhibitors of GLUT I function

→ Phenobarbital, Chloralhydrate, Diazepam

→ Methylxanthines: theophyllin, caffeine,

→ Triciclic antidepresants, Alcohol, Green tea

→ High-carbohydrate diet +/- hyperglycemic agent (diazoxide)

Pediatric Neurology 53 (2015) 243e246

Clinical Observations

New Paradigm for the Treatment of Glucose Transporter 1 Deficiency Syndrome: Low Glycemic Index Diet and Modified High Amylopectin Cornstarch

Mohammed Almuqbil MD [a,b,c], Cristina Go MD [d], Laura L. Nagy MSc, RD [a,e], Nisha Pai MSc, RD [a,e], Eva Mamak PhD [f], Saadet Mercimek-Mahmutoglu MD, PhD [a,g,*]

Case History

- GA: 39 weeks , c/s: preeclampsia
- BW: 3375 gr HC: 34 cm
- Family: mother : Luxembourg
  father : Iran
  seizures, consanguinity

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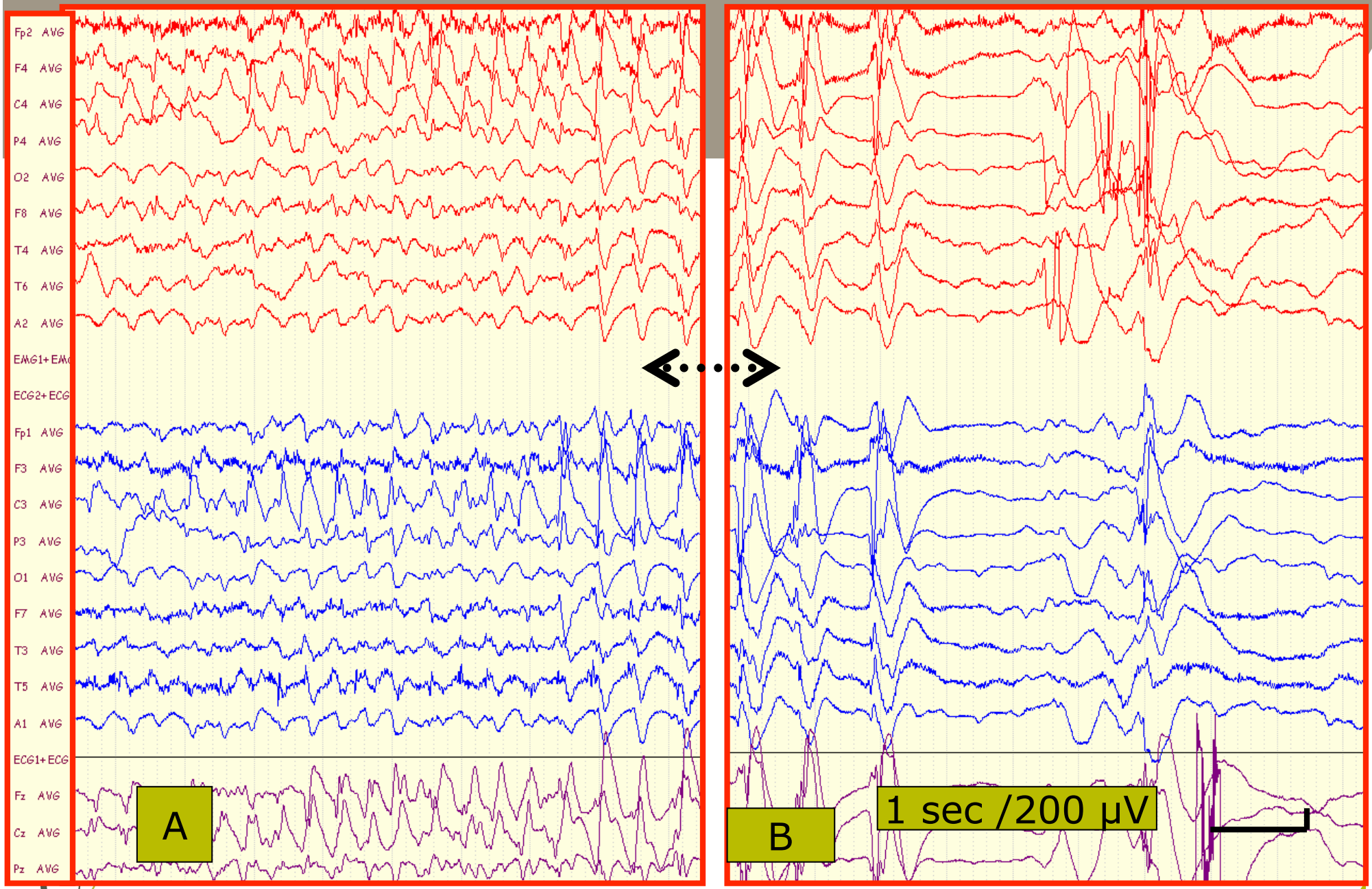
Case
2 ½ months

- Admitted for episodes of seizures described as extension of the arms, hyperextension of head, 15 sec with staring ; 3-5 a day
- Psychomotor development a little slow, not yet fixating well
- On admission axial hypotonia and peripheral hypertonia
- Skin and hair normal



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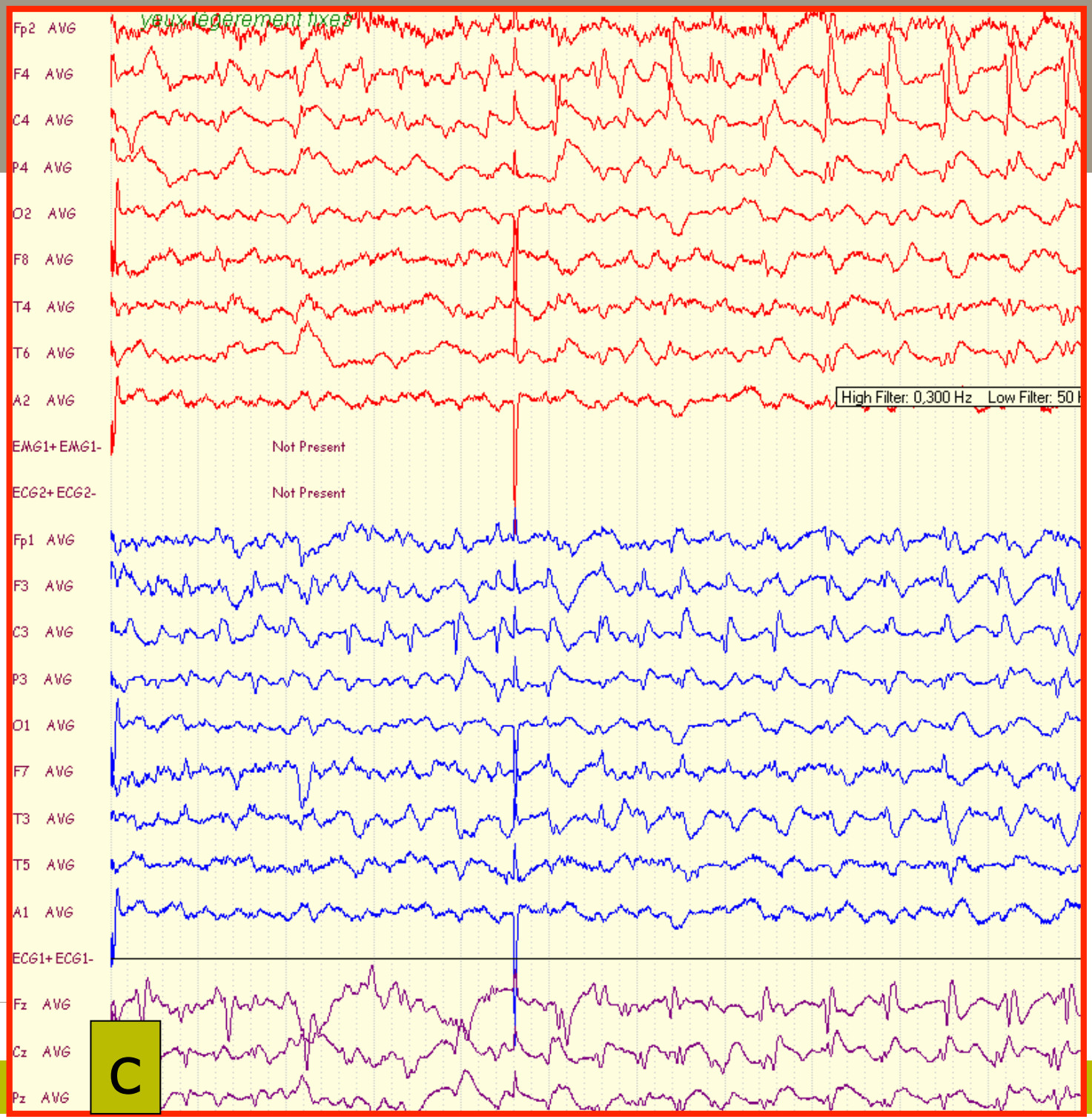
Day one



Day one

1 sec /200 µV

18-04-2017

Investigations

- Lactate 23mg/dl CSF lactate 43.3 mg/dl
- MRI edema white matter
- EEG spikes and spike waves starting frontal then generalisation; interictal spikes frontal
- No reaction on phenobarbital, topamax, diphantoine
- Metabolic screening : acylcarnitines 3-OH isovalerylcarnitine elevated
- Organic acids : 3 OH isovaleric aciduria
- DIAGNOSIS?

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Biotinidase deficiency

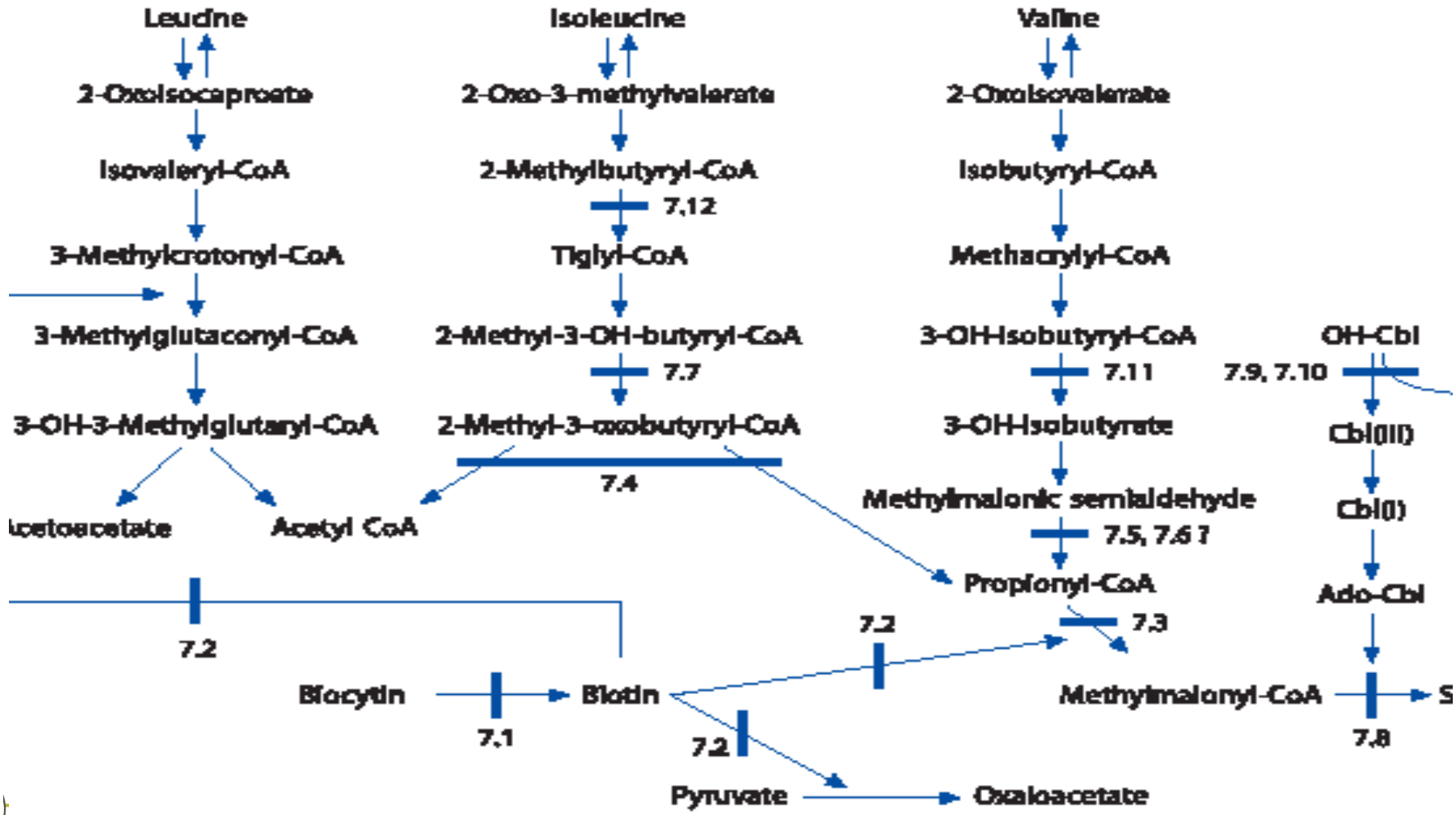
- start biotine 10mg po
- stop of all seizures
- all antiepileptics discontinued
- at 6 months : normal development

biotine

- defect in biotinidase
  - → seizures start first three months of life, myoclonia,
  - → often infantile spasms
  - → optic atrophy
  - → atopic dermatitis, alopecia
  - → hypotonia

  - → 5-10mg per day of biotine

Pathways of valine and isoleucine



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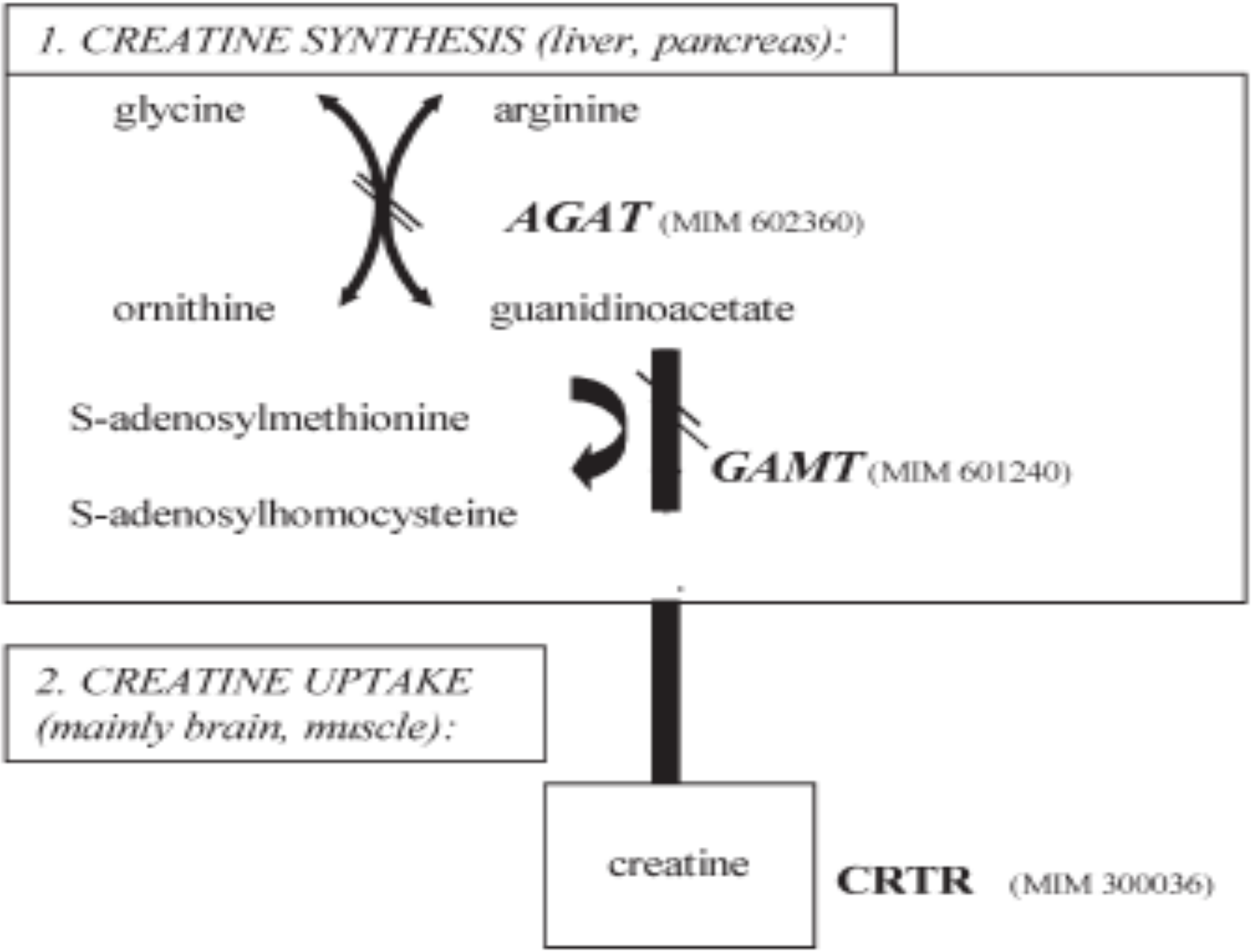

1. CREATINE SYNTHESIS (liver, pancreas):
glycine
arginine
AGAT (MIM 602360)
ornithine
guanidinoacetate
S-adenosylmethionine
GAMT (MIM 601240)
S-adenosylhomocysteine
2. CREATINE UPTAKE
(mainly brain, muscle):
creatine
CRTR (MIM 300036)

Creatine metabolism

- three different defects
  - →GAMT (guanidinoacetate methyltransferase)
  - →AGAT (arginine-glycine amidinotransferase)
  - →X-linked creatine transporter

- creatine supplementation, dietary reduction of arginine and supplementation of ornithine to control seizures

Creatine transporter X-linked

- **Biochemical**
- 1H-MRS brain - absence of creatine signal
- Severe depletion creatine/phosphocreatine in brain
- Increased creatine in plasma and urine, GAA normal

- **Genetics**
- SLC6A8 gene maps to Xq28

Creatine transporter

Treatment

- Creatine supplementation - does not correct cerebral creatine deficiency
- L-arginine (substrate for AGAT) no improvement in speech, behaviour, motor skills or brain creatine
- 1 year therapy with L-arginine in 9 year old, found improvement in neurological, language and behavioural status and increased brain creatine
- Lysine and SAM

Genetics

- SLC6A8 gene maps to Xq28
- Hemizygous mutations

Creatine metabolism Diagnosis

- Guanidoacetate and creatine
  →in urine and CSF

- ABSENT CREATINE AND CREATINE PHOSPHATE PEAK ON MRS

X-linked and developmental delay

Creatine transporter

Lesh Nyhan

FraX

Menkes disease

MCT8

Occipital horn syndrome

Pelizeaeus -Merzbacher

Joe

- feeding difficulties first month
- hypotonia
- slow development
- intermittent dyskinesia
- developing quadriplegia
- first MRI negative
- 2nd MRI at 12 months delay in myelination

Joe

- mother had a brother who died of Cerebral palsy at age 10 years
- T3 elevated, mutation in MCT8
- So delay in myelination plus increased T3 - → MCT8 transporter defect

Allan-Herndon- Dudley syndrome

- severe intelectual disability
- X linked
- dysarthria, athetoid movements
- spastic quadriplegia
- high serum free T3 levels
- mutations in the MCT8 gene coding for the monocarboxylate thyroid hormone transporter 8

Clue to diagnosis

- Thyroid testing
  - → FT4: 0,6ng/dl (nl: 1,0-1,8) ↓
  - → FT3: 6,5pg/ml (nl: 2,4-5,5) ↑↑
  - → TSH: 2,4mU/l (nl: 0,70-6,0) =

Male with developmental delay (axial hypotonia) + typical thyroid test abnormalities

➔ suggestive for Allan-Herndon-Dudley syndrome

MCT8 analysis: c.812G>A, p.R271H

MCT8 deficiency

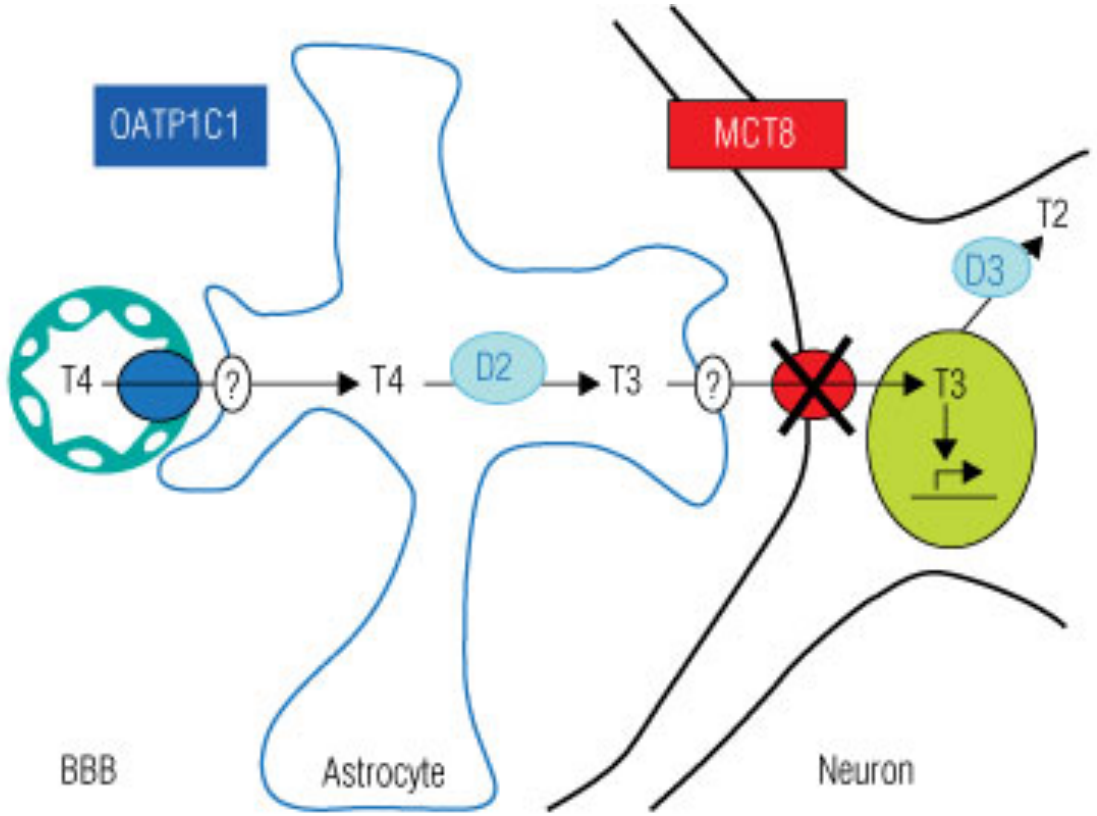


Figure 1. Simplified schema of the regulation of T3 supply to neuronal target cells in brain, and the defect induced by MCT8 mutation.

Trial Triac (Visser Rotterdam)

- T3 analog Triac (Tiratricol)

- to normalise T3 levels
- should lead to reduction of symptoms such as failure to thrive, insomnia
- increase of T3 in neurons to improve neurological outcome
- 12 month study with escalating dose of Triac until T3 normalises

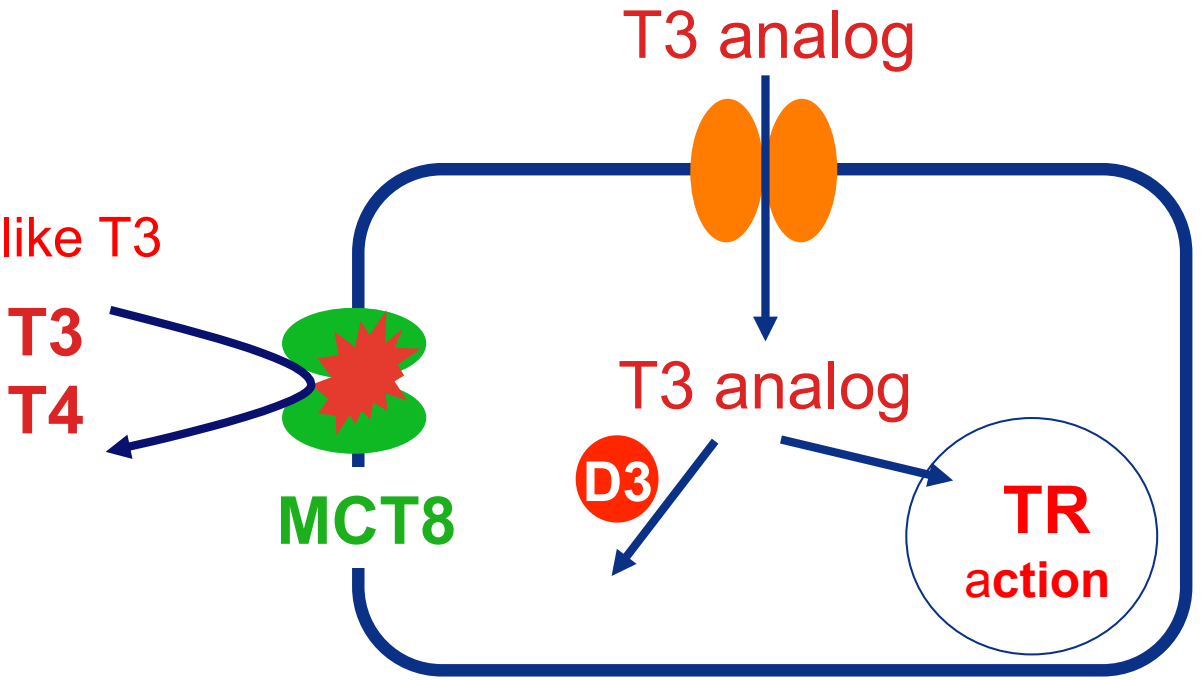
T3 analog (Triac) therapy

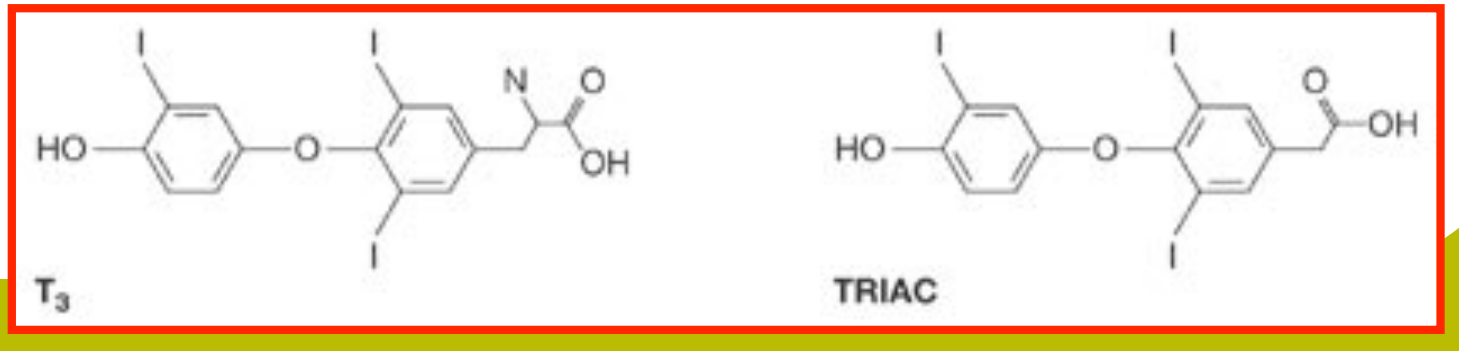
Requirements

1. Bypass MCT8

2. Act like T3

3. Degradation pathways like T3





TRIAC TRIAL
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Recent developments

- Glut 1 transporter
- Folate transporter(s)
- Riboflavine transporter
- Thiamine transporter (s)
- Dopamine transporter

Folate receptor defect

→clinical hallmarks of the disease

- psychomotor regression with ataxia
- myoclonic epilepsy
- autism
- disturbances of myelination

→Low 5 MTHF in CSF

→Potentially treatable

→Long-term outcome remains unknown

Folate receptor alpha defect causes cerebral folate transport deficiency (Steinfeld R *et al*, …)

- 2 siblings
  - →Oral folinic acid treatment
  - →Boy 3 yrs 9 m : ⇓ frequency and severity of epileptic seizures, started to walk with support
  - →sister, younger by 2 years, treated with folinic acid directly after onset of first motor symptoms, at age of 2 years and 3 months
  - →completely recovered and has not developed clinical symptoms
- 3rd patient at age of 5 years : severely handicapped, frequent epileptic seizures; clinical condition slowly improved with treatment

Thiamine transporter

- A wide spectrum of clinical and brain MRI
- findings in patients with SLC19A3 mutations
- Kenichiro et al,

BMC Medical Genetics 2010, 11:171

Thiamine transporter

- epileptic spasms appeared in infancy in all patients
- in contrast to the epilepsy onset in childhood for patients with BBGD

- MRI findings
  - → progressive brain atrophy
  - → lesions in the bilateral thalami
  - → patients did not display dystonia and cogwheel rigidity
  - → high dose of biotin for one year improved neither the neurological symptoms nor the brain MRI

- unclear whether administration of biotin at early stages of the disorder (when epileptic spasms first appeared) improved the subsequent clinical trajectory

Ortigoza-Escobar et al. Orphanet Journal of Rare Diseases 2014, 9:92
http://www.ojrd.com/content/9/1/92

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Thiamine transporter-2 deficiency: outcome and treatment monitoring

Juan Darío Ortigoza-Escobar[1], Mercedes Serrano[1,5], Marta Molero[2,5], Alfonso Oyarzabal[4,5], Mónica Rebollo[3], Jordi Muchart[3], Rafael Artuch[2,5], Pilar Rodríguez-Pombo[4,5] and Belén Pérez-Dueñas[1,5*]

Abstract

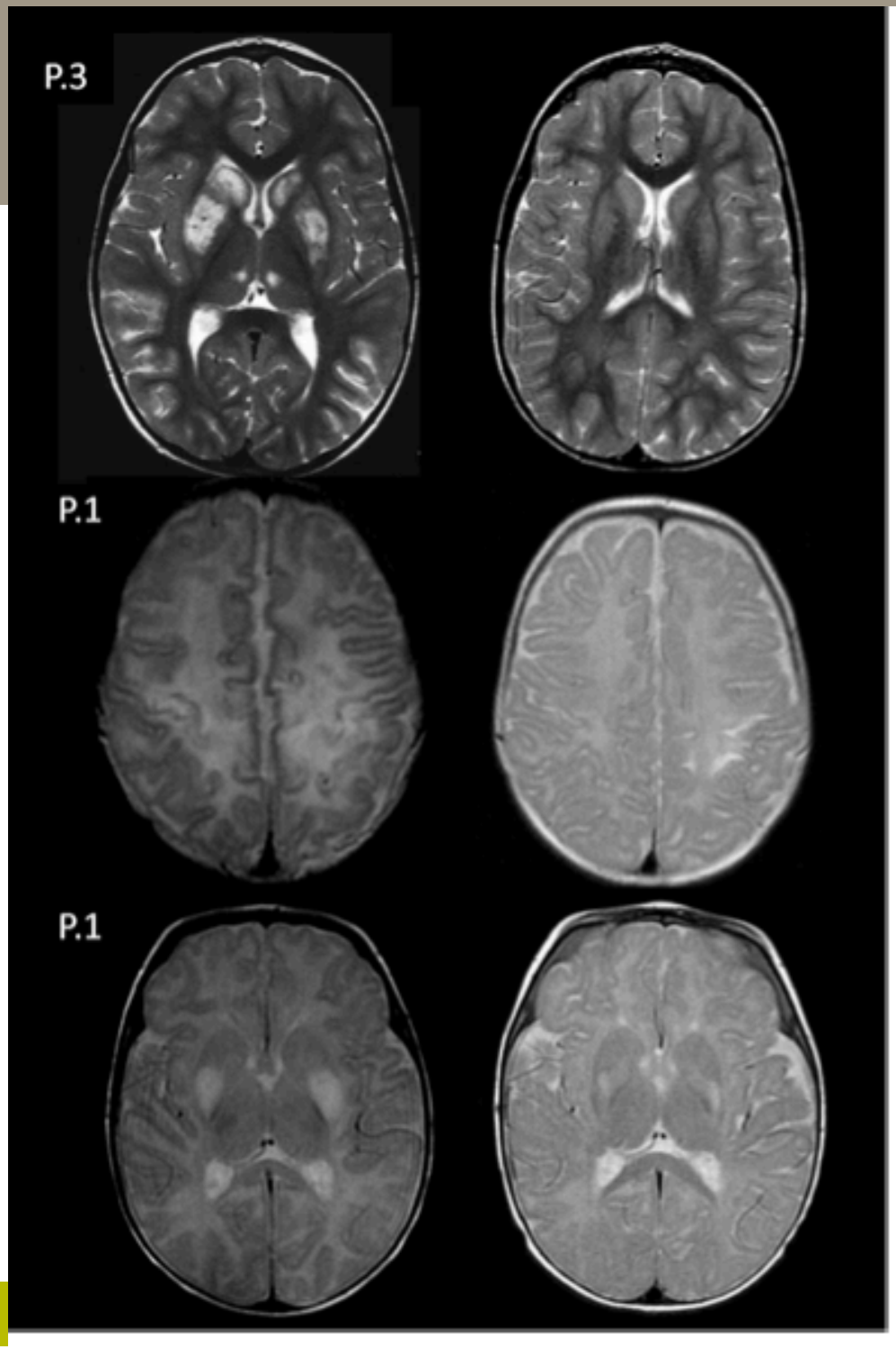
Thiamine responsive Leigh

- follow-up after thiamine and biotin supplementation in four children with ThTR2 deficiency

- Leigh and biotin-thiamine-responsive basal ganglia disease phenotypes

Leigh and thiamine transporter

- 1 month to 17 years
- All acute encephalopathy, generalized dystonia, and brain lesions affecting dorsal striatum and medial thalami
- clinical and radiological improvements shortly after initiation of thiamine
- thiamine (10–40 mg/kg/day) + biotin (1–2 mg/kg/day)
- remained stable with residual dystonia and speech difficulties



Pre and post treatment

Lysomal storage diseases and treatment

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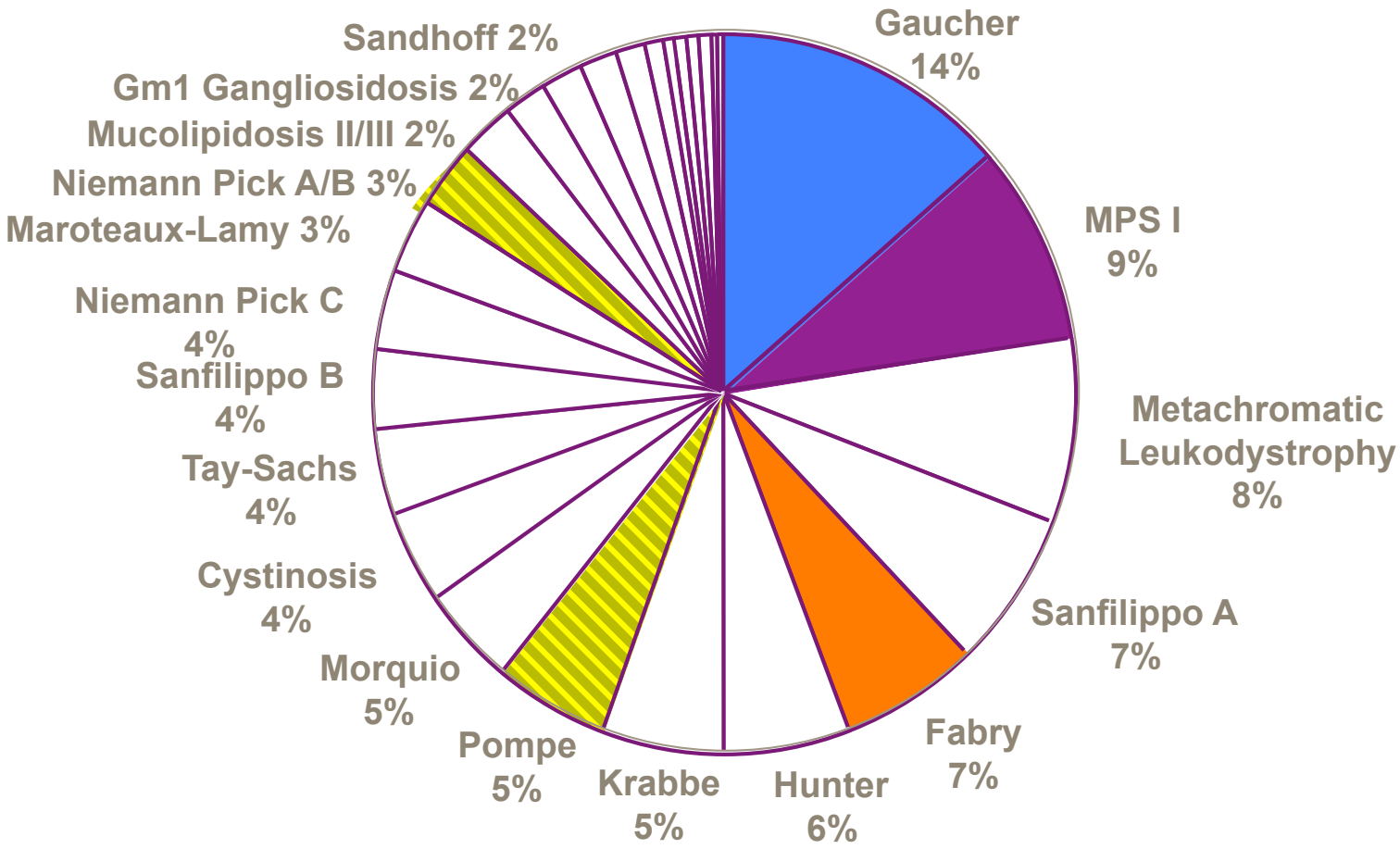
LYSOSOMAL STORAGE DISORDERS (based on neonatal screening)



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(For Australia1980-1996; Meikle et al., 1999)

LSD subdivision

Sphingolipidoses

Failure to degrade glycosphingolipids containing three or less carbohydrate residues.

Fabry, Gaucher, ASM deficiency (Niemann Pick A,B), Metachromatic Leukodystrophy, Krabbe,….

Mucopolysaccharidoses

Failure to degrade glycosaminoglycans

MPS I (Hurler, Hurler Scheie, Scheie), Hunter, San Filippo, Morquio, Maroteaux-Lamy, …

Oligosaccharidoses

Failure to degrade oligosaccharides

Fucosidosis, Mannosidosis, Sialidosis, Galactosialidosis,…

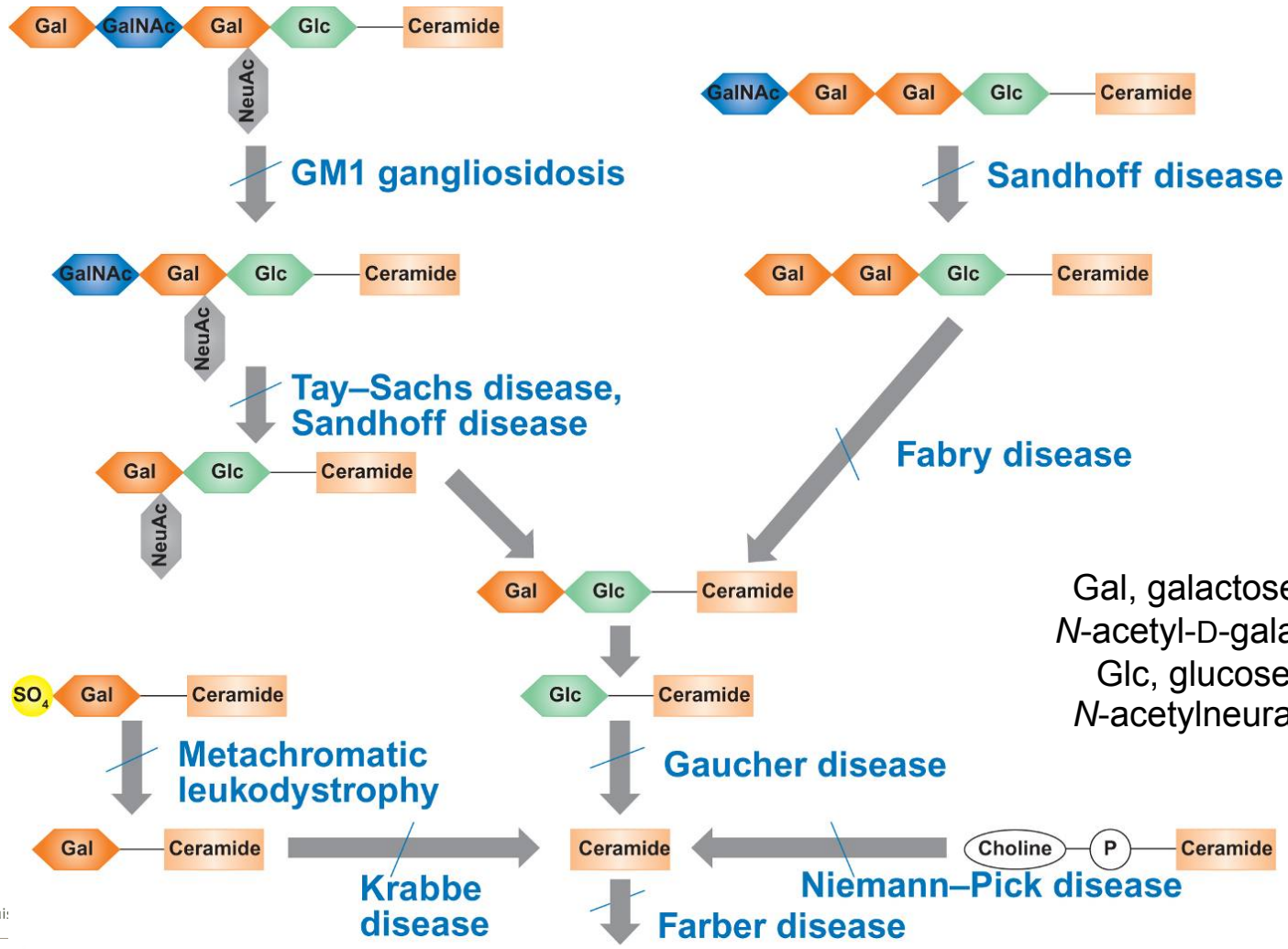
Others

Pompe, Mucolipidosis, Ceroid lipofuscinosis, …

:sel

For reference, please see notes

Defects in a single metabolic pathway lead to different lysosomal storage diseases



Gal, galactose; GalNAc, *N*-acetyl-D-galactosamine; Glc, glucose; NeuAc, *N*-acetylneuraminic acid

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Reproduced from Beck & Ries, *Fabry disease: clinical manifestations, diagnosis and therapy*. Oxford: OCC Europe Ltd; 2001 with permission

Enzyme replacement therapy

- Gaucher's disease
- Fabry's disease
- MPS I (Hurler – Scheie)
- MPS IV (Morquio)
- Pompe's disease
- MPS II (Hunter)
- MPS VI (Maroteaux-Lamy)

new Niemann-Pick B ; alpha mannosidosis; MPS IIIA; MPS IIIB

Treatment strategies for lysosomal storage diseases

- Bone marrow/ umbilical cord transplantation
- ERT (enzyme replacement therapy)
- ERT-IT

- Substrate reduction
- Chaperone therapy
- Cell transplantation
- Gene therapy
- >>> EARLY DIAGNOSIS

Multi-systemic

MPS

Lysosomale storage of GAG in many tissues

- CNS
- nose, throat, ears
- eyes
- teeth
- airways
- heart and blood vessels
- gastrointestinal system
- joints
- bones
- peripheral nervous system
- other

MPS I spectrum of disease

SEVER — ATTENUATED

HURLER — HURLER-SCHEIE — SCHEIE

	HURLER	HURLER-SCHEIE	SCHEIE
Age at diagnosis	0.2–7 years	0.2–36 years	2–54 years
Effect on cognition	Pronounced mental delay with loss of acquired skills	No/mild mental delay; learning disabilities	No impairment
Mean life expectancy (untreated)	7 years	Approximately 20 years	Adulthood
Phenotype distribution*	~65%	~25%	~10%

*Estimates based on Moore et al. Orphanet J Rare Dis 2008;3:24 and MPS I Registry data

Hematopoietic stem cell transplantation

> 400 MPS I severe form transplanted

- CNS relies on infiltration by donor macrophages
- enzymes secreted into the bloodstream by donor
- Eraly treatment best outcome

MPS1 Hurler, Scheie, Hurler-Scheie

- Autosomal recessive disease
- Defect in lysosomal α-L-iduronidase
- Defect in degradation of glycosoaminoglycans (GAGs), dermatansulfate and heparansulfate
- Progressive accumulation > cell /organ dysfunction
- 1/100.000
- 50% +CNS

Signs and symptoms

Lisa

- 3 month FTT
- Mild axial hypotonia
- No hepatosplenomegaly
- MRI brain; liverultrasound negative
- improved
- ENT infections and hearing loss
- urine MPS positive
- MPS type 1

Glenn

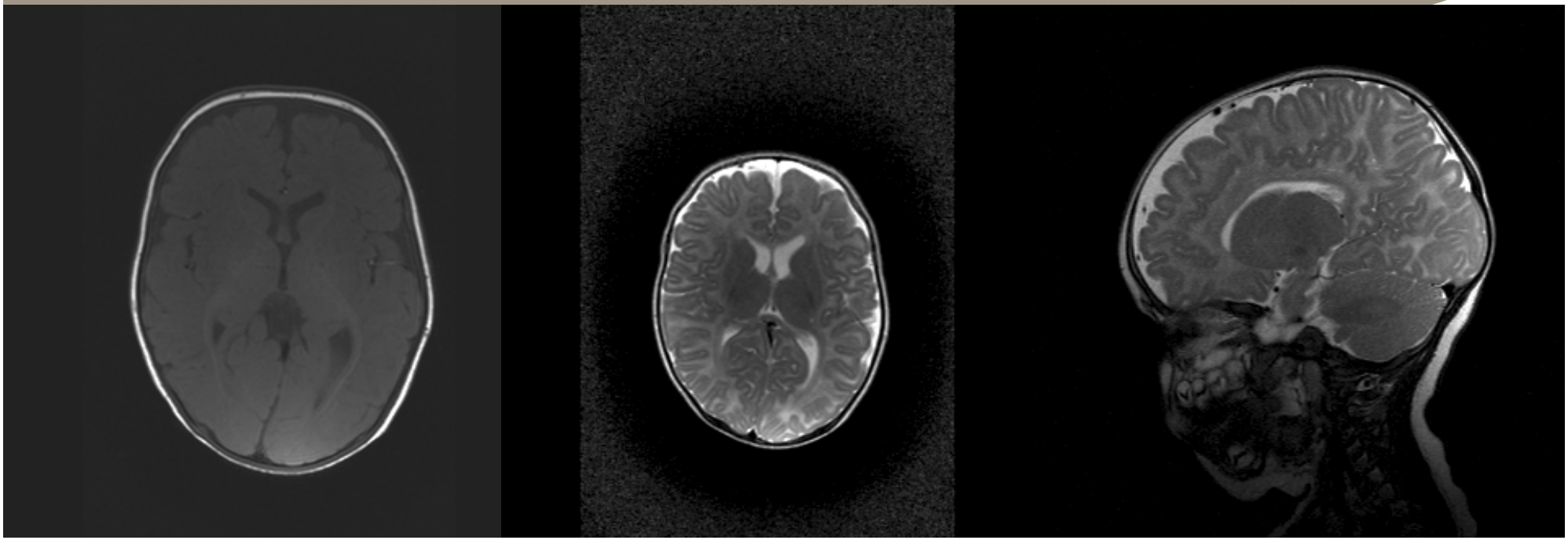
- No familial history
- Hearing loss and frequent ENT infections
- Two operations for inguinal hernia
- Mild delay in development
- ENT does MPS urine screening
- urine MPS positive
- MPS type 1

Evolution

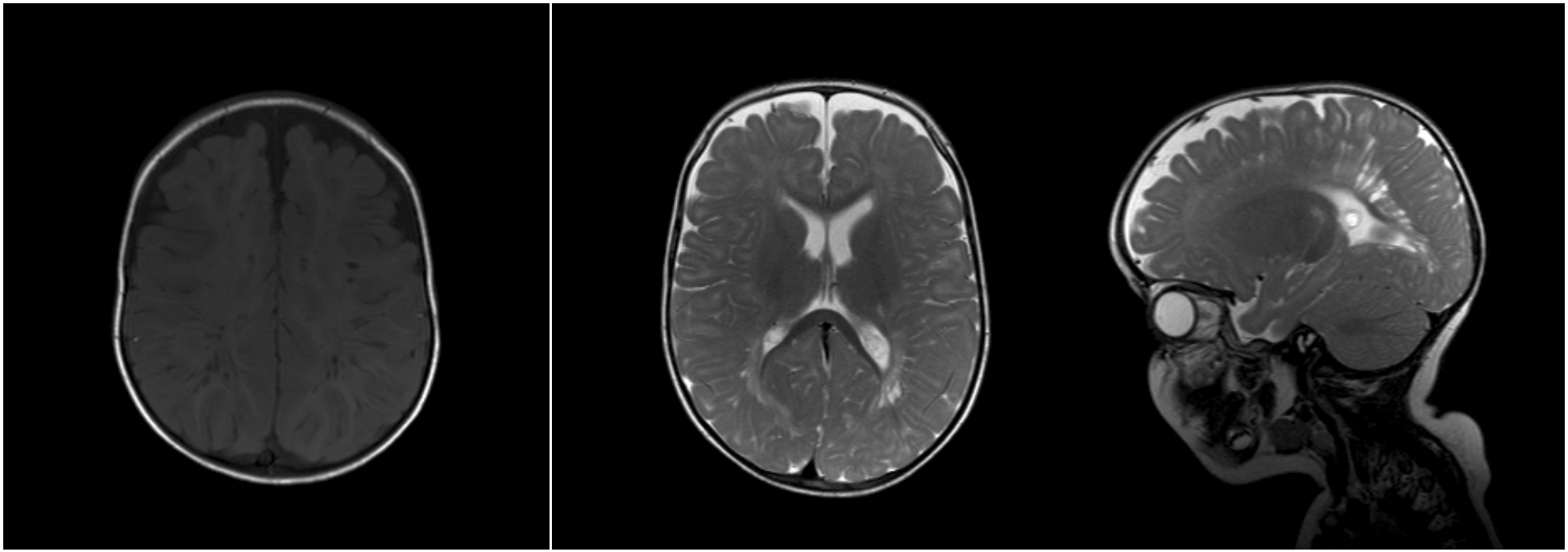
- Start ERT
- Echocardio normal
- Bonemarrow transplantation at 11months
- Good cognitive outcome

- Start with ERT
- Bone marrow transplantation at 12m
- Good cognitive outcome

MRI at 3 months



MRI at 12 months



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Pitfalls in diagnosis

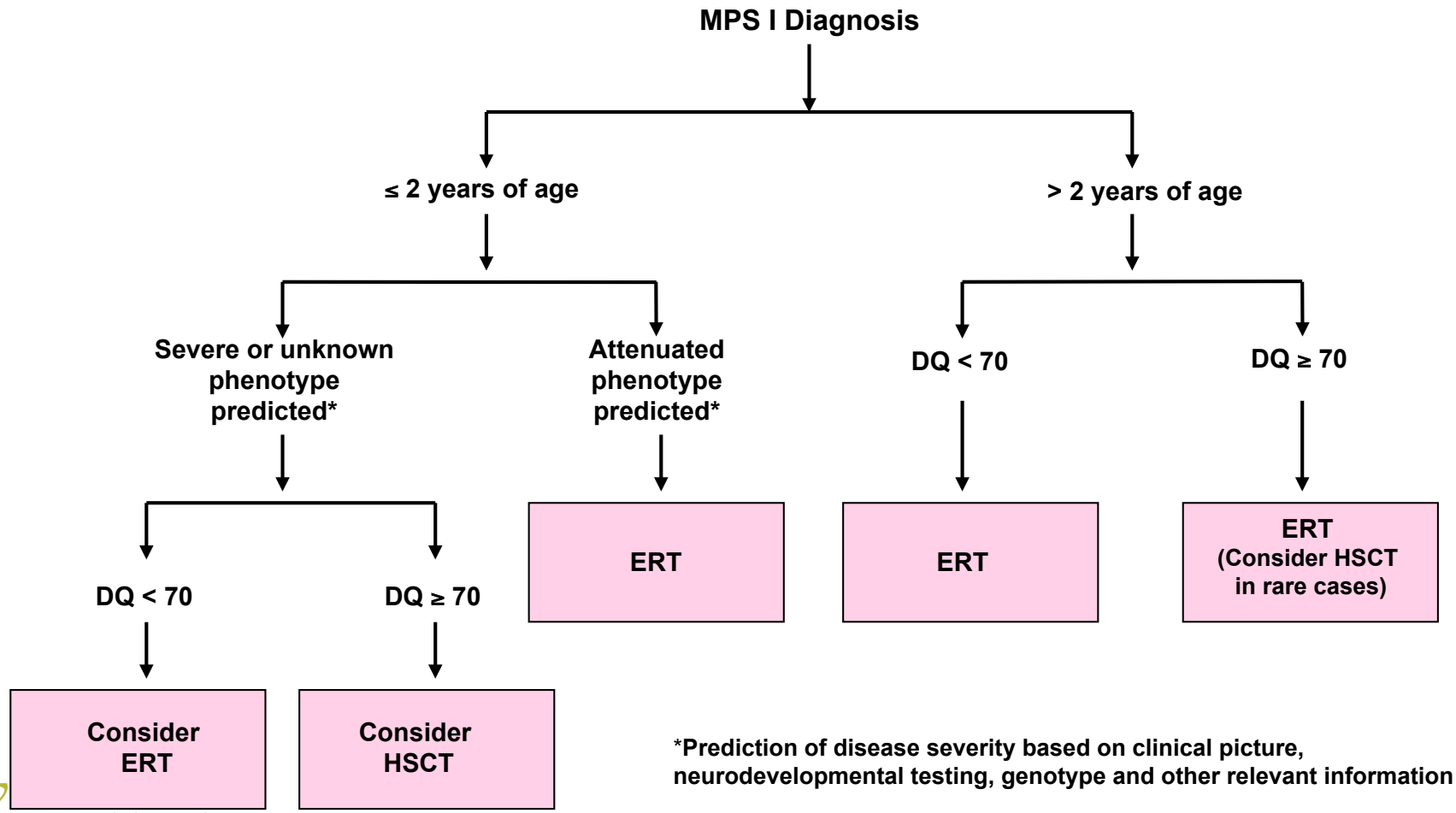
- ENT specialist
- pediatrician, gastroenterologist
- pediatric surgeon
- orthopedic surgeon
- Pediatric neurologist?

- Diagnosis EASY : URINE for GAGS

ERT and MPS1

- Improvement on hepatosplenomegaly
- Improvement of cardiac and respiratory functions
- Improvement of sleep
- Improvement of growth
- Improvement of mobility of joints
- Skeletal deformities and CNS involvement remain a problem
- EARLY DIAGNOSIS BETTER PROGNOSIS

Treatment algorithm for MPS I



*Prediction of disease severity based on clinical picture, neurodevelopmental testing, genotype and other relevant information

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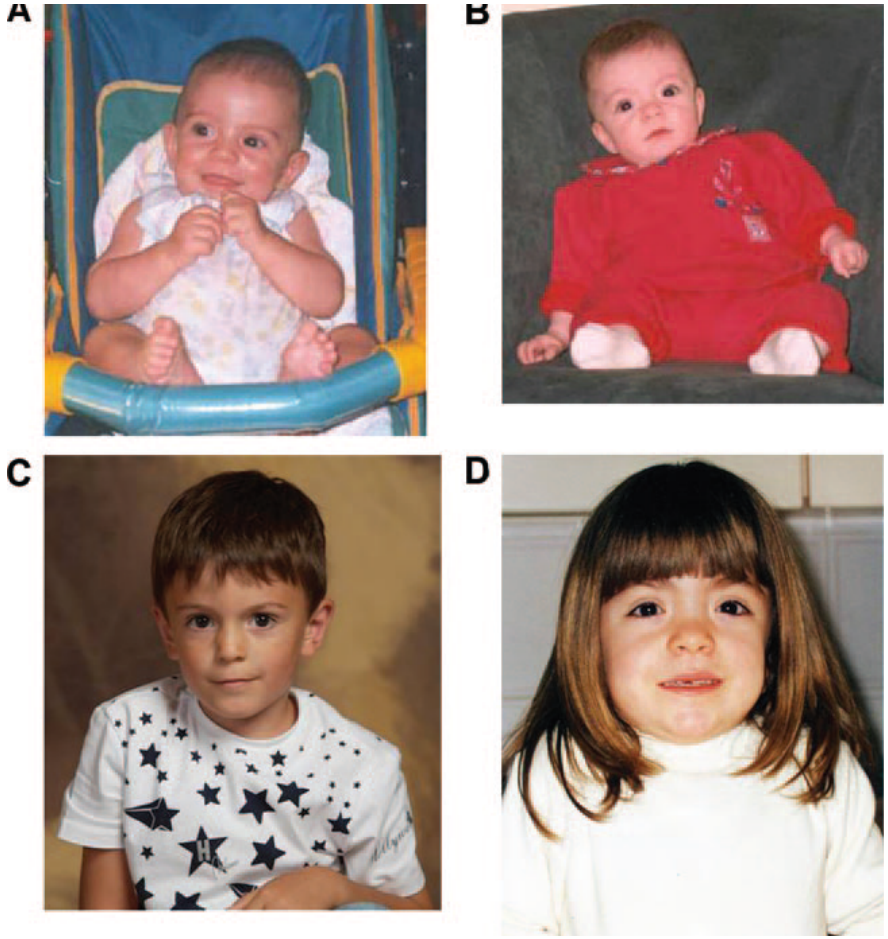
[1]From Muenzer et al. Pediatrics 2009;123:19-29

Physical appearance of the siblings.
A Patient M at 5 months of age right before he began laronidase treatment.
B Patient F at 5 months of age, 4 years before her MPS I diagnosis.
C Patient M, age 5.5 after 5years of laronidase.
D Patient F at age 5, right before she began laronidase treatment.



www.pediatrics.org/cgi/doi/10.1542/peds.2009-1728

Multidisciplinary follow-up and management attenuated MPS1

- Visual and hearing aids
- Corneal grafting
- Valvular replacement
- **CAVE anaesthesia!!!**
  - → Instability of atlantoaxial joint
  - → Inability to maintain adequate airway
  - → Narrowed trachea and thickened vocal cords

- Enzyme replacement

Multidisciplinary follow-up and managementin MPS1

- Neurosurgery
  - → Hydrocephalus
  - → Carpal tunnel decompression
  - → Spinal cord decompression
- Orthopaedics
  - → Vertebral stabilization
  - → Joint replacement
- Tonsillectomy, CPAP, tracheotomy
- ENT ventilation ear tubes

MPS1 severe form

- Early recognition
- Increase Awareness
- Need for neonatal screening or other screening studies

Case

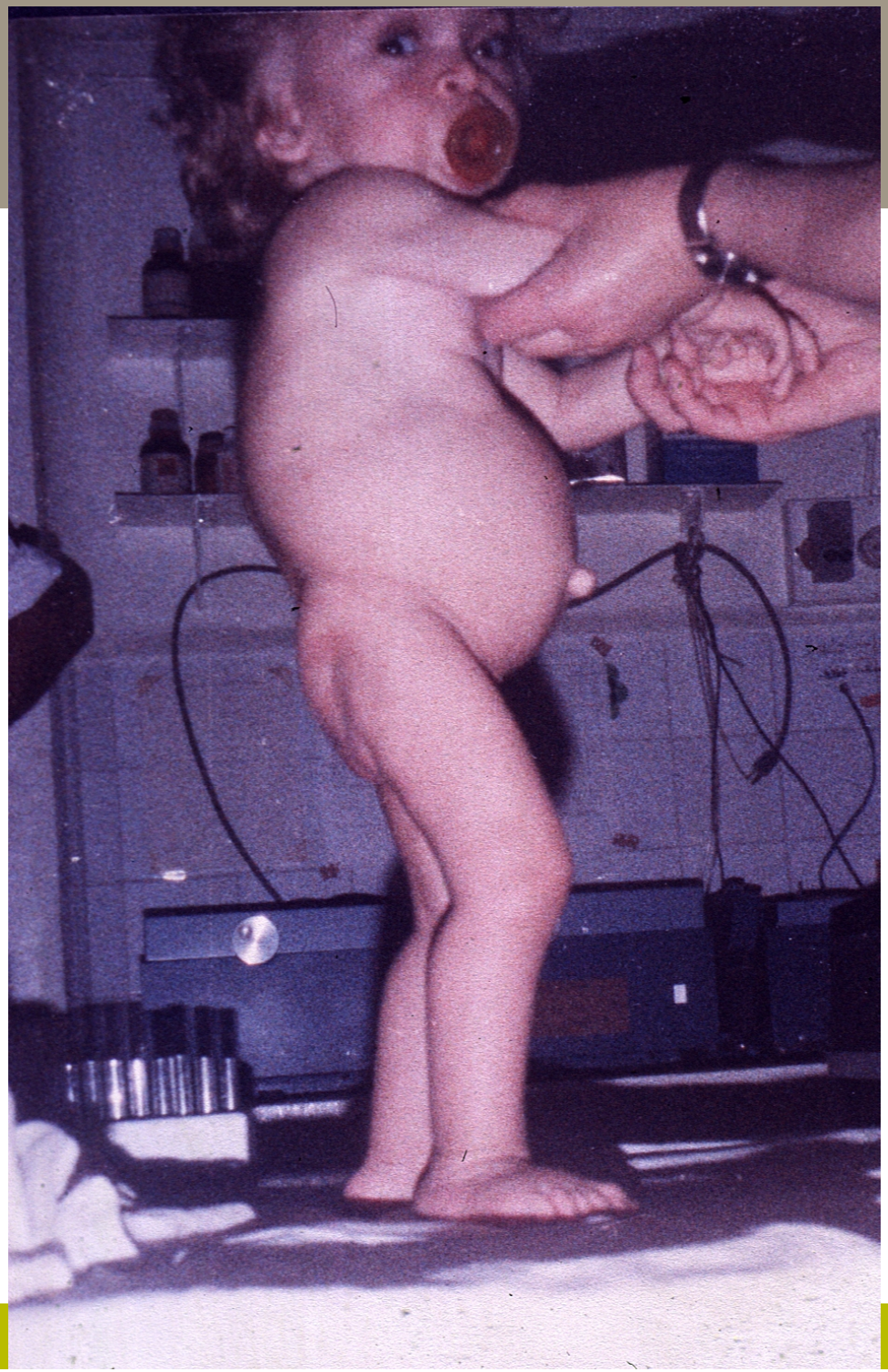
- girl diagnosed with MPS I at the age of 2 years 6 m
- Weekly intravenous Aldurazyme since the age of 4 years
- Macrocephaly; kyphosis; clouding of cornea
- Liver 14 cm, spleen 7 cm
- Global psychomotor delay
- Active child with good communication skills
- MRI lesions white matter and storage
- Echocardiography
  - → mitral valve insufficiency secondary to thickened mitral valves
  - → thickening of pulmonary valve cusps
- ABRs 90/70 db

After 24 months of treatment with ERT

- Parents
  - →better general condition
  - →improved sleep
  - →improved mobility
- Hearing improved with hearing aids

After 24 months of treatment

- MOS at 5 years 1 m = 2 years 9 m (< 50)
- But performance 3 years 9 months
- Perception deafness 55–65 db
- Social and cooperative
- Stiffness unchanged
- However, pyramidal tract signs in lower limbs



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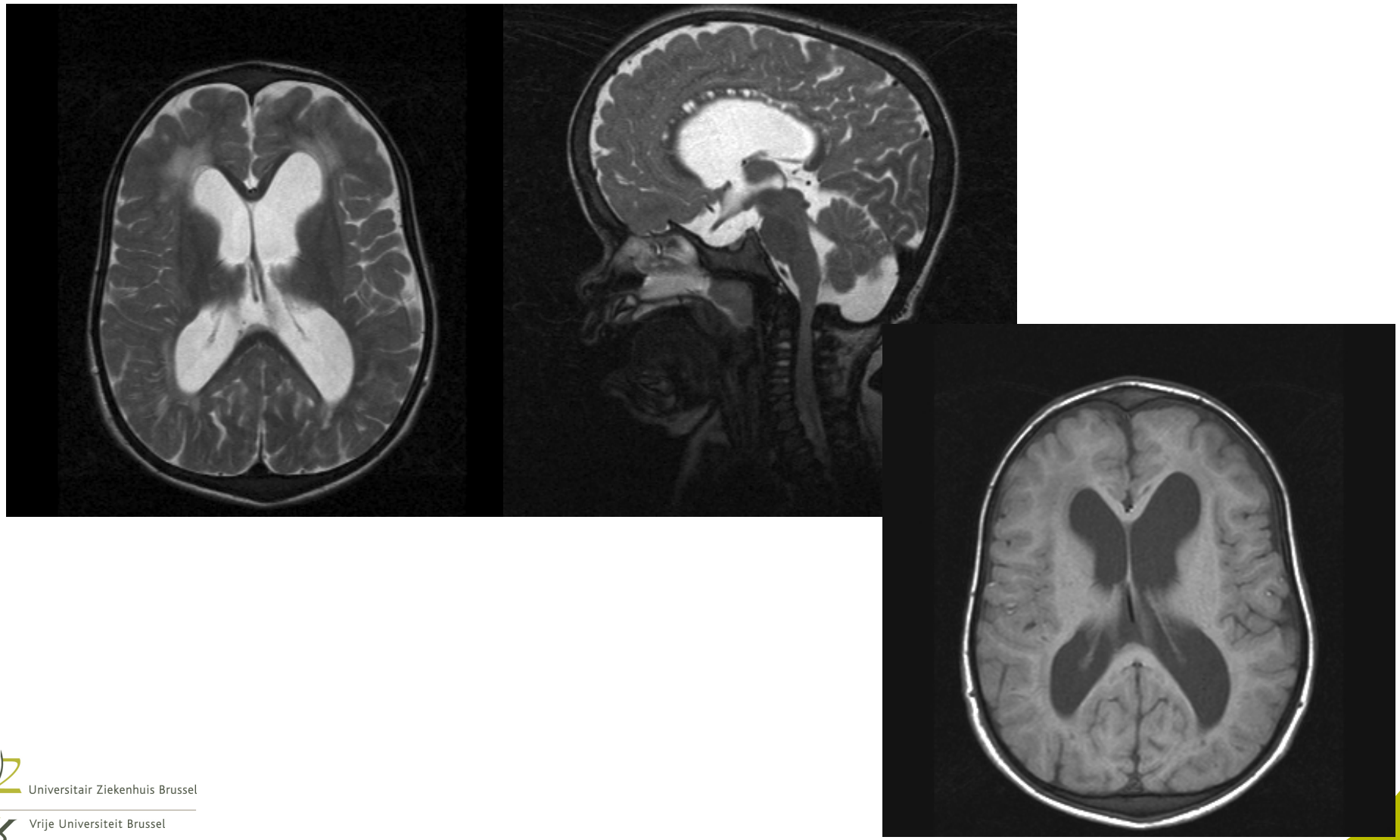
Evolution

At the age of 6 years, she developed episodic hemiplegia with certain head movements.

An MRI of the posterior fossa revealed compression of medulla and cervical cord due to meningeal thickening

2004



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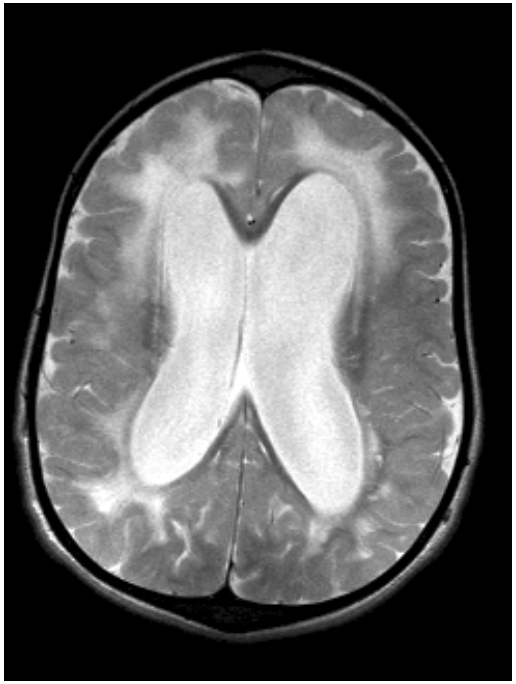
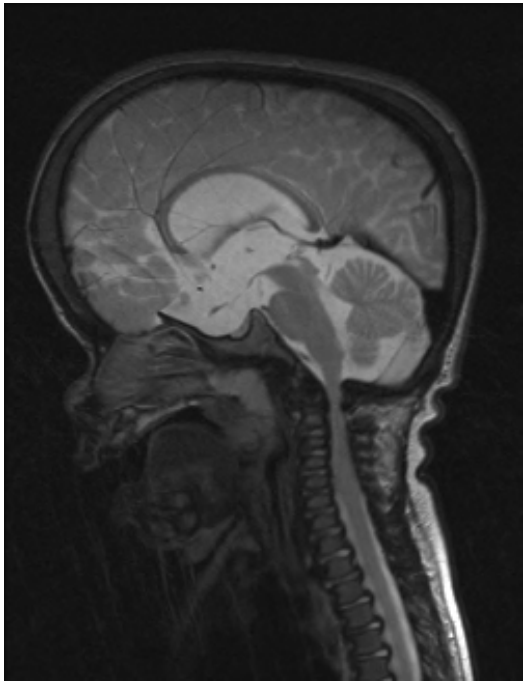
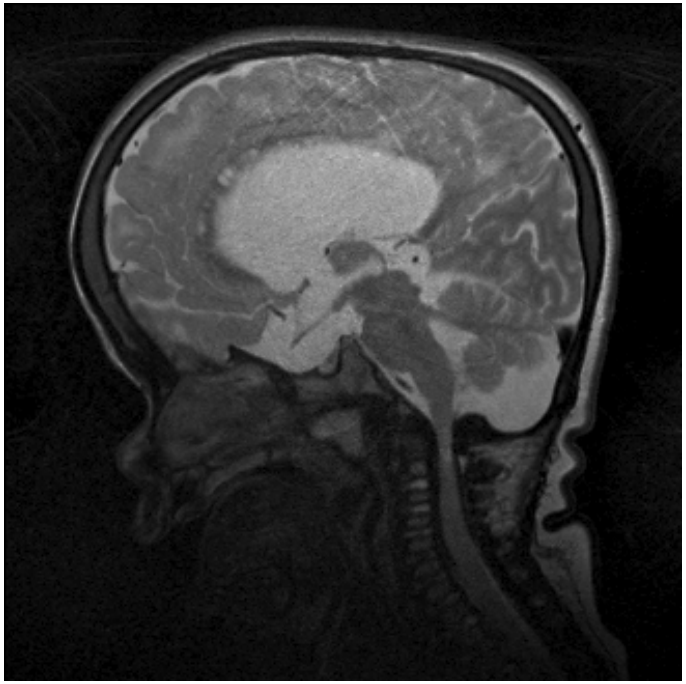
2005







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Intrathecal Aldurazyme

- Using a protocol proposed by P Dickson (LA, CA, USA) intrathecal enzyme solution was started at the age of 6.5 years by monthly lumbar punctures
- This was continued for 5 years

Comments on intrathecal Aldurazyme

- No side-effects were noted during or after
- Intrathecal injections monthly continuing for more than 5 years
- CSF protein levels

  →decreased but did not normalize
- GAGs in CSF were not found
- Clinically the child stabilized
- Had no further episodes of sudden aggravation with hemiplegia

Conclusion

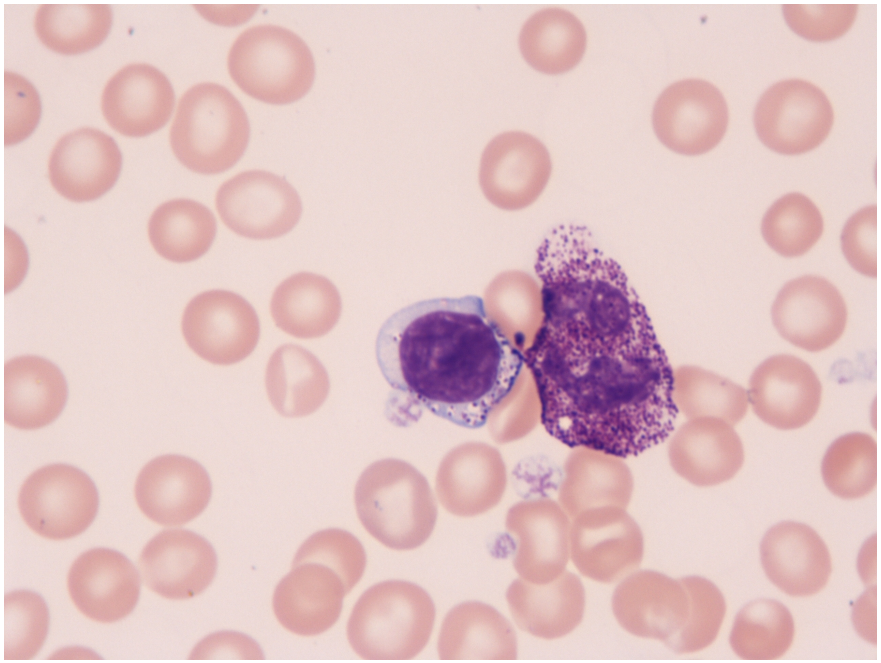
- Early onset MPS I needs early diagnosis in order to start ERT and bone marrow transplantation
- Intrathecal Aldurazyme can be helpful in stabilizing patients with cervical cord compressoion
- Intrathecal Aldurazyme does not lead to important side-effects

Case

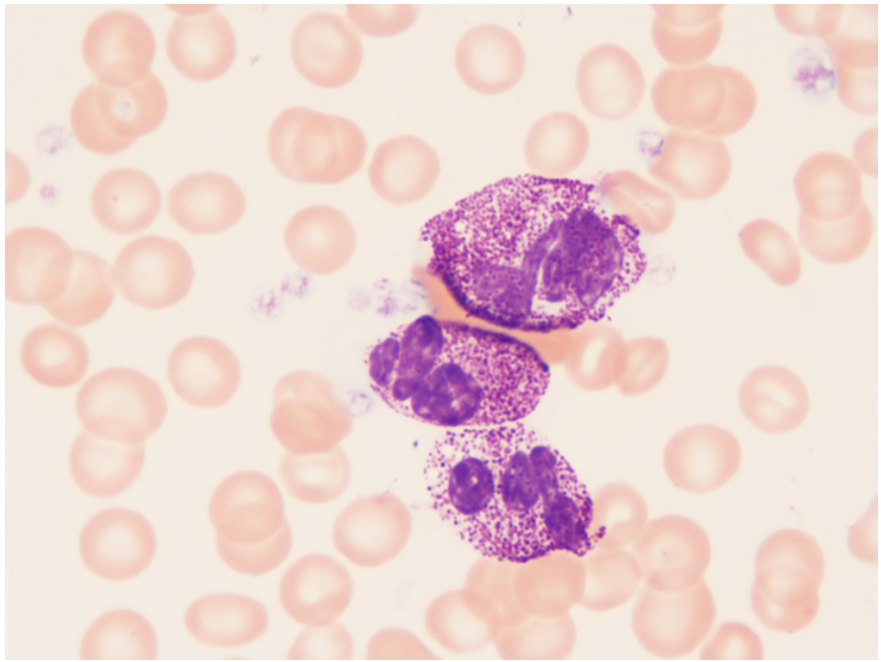
- 17 month old girl African descent
- Normal pregnancy
- Mild delay in motor development
- Constant colds, snoring, coughing first year of life
- Pediatrician: hematological examination

-→ vacuolated lymphocytes

Hemato



Lymphocytes de Gasser



granulocytes azurofiele korrels (=anomaly van Alder-Reilly).

Physical Examination

- Mild dysmorphism
- Mild kyfosis lumbar spine
- Large hands
- Impression of cornea clouding
- No hepatosplenomegaly
- No contractures
- MPS urine positive; diagnosis
- →Maroteaux-Lamy MPS 6; started on ERT

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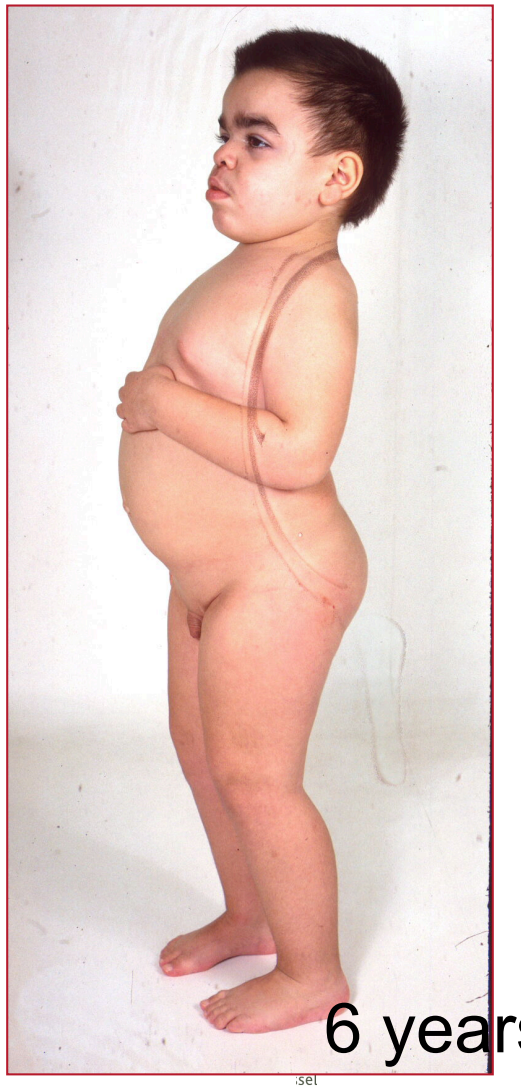
Major Charles Hunter CAMC MD 1917

A Rare Disease in Two Brothers

- Brothers 10 and 8 years
- Hearing loss
- Short stature
- Large heads
- Cardiomegaly
- Umbilical hernia
- Joint stiffness
- Dysostosis multiplex
- Died at 11 and 16 years - cardiac disease

Variable Phenotypic Expression Hunter



Early signs and symptoms
First years of life

- recurrent ear infections
- chronic nasal discharge
- trouble breathing
- umbilical or inguinal hernias
- hepatosplenomegaly and enlarged abdomen
- skeletal abnormalities

Hunter: Natural history

- **Most common symptoms**

- 95% joint stiffness
- 93% clawed hands
- 87% hepatomegaly
- 86% valve disease
- 83% otitis media
- 81% enlarged tongue
- 80% conductive hearing loss
- 78% sensory/neuro hearing loss

- **Other symptoms of disease**

- 75% splenomegaly
- 69% enlarged tonsils
- 66% enlarged adenoids
- 52% mental /psychomotor retardation

- **Average age of disease onset was 2.3 years**

- 2.7 years for attenuated
- 1.9 years for severe patients

- **Average age of diagnosis was 3.9 years**

- 4.3 years for attenuated
- 3.5 years for severe patients

:sel

Treatment Hunter's disease

- ERT in attenuated form
- No good result with bonemarrow transplantation
- Symptomatic
- Multidisciplinary follow-up

Enzyme replacement therapy

- Gaucher's disease Non-neuronopathic
- Fabry's disease
- MPS I (Hurler – Scheie; Scheie)
- Pompe's disease
- MPS II (Hunter)
- MPS VI (Maroteaux-Lamy)
- MPS IV (Morquio)

Trials Niemann-Pick B

alpha mannosidosis

MPSIIIA

New treatments

MLD several gene therapy studies but in early onset asymptomatic;

MLD juvenile bone marrow indicated if early

Genen therapy in NCL2 or enzyme in the brain

Chemical chaperones

- misfolded enzymes rapidly degrade by proteasomes
- chaperones can increase residual enzymatic activity by rescuing misfolded mutant proteins from rapid endoplasmatic reticulum associated degradation
- 10% activity can prevent storage
- can cross the BBB
- several molecules have been developped for MPSIIIIB

Small molecules active-site specific chaperones (ASSC)

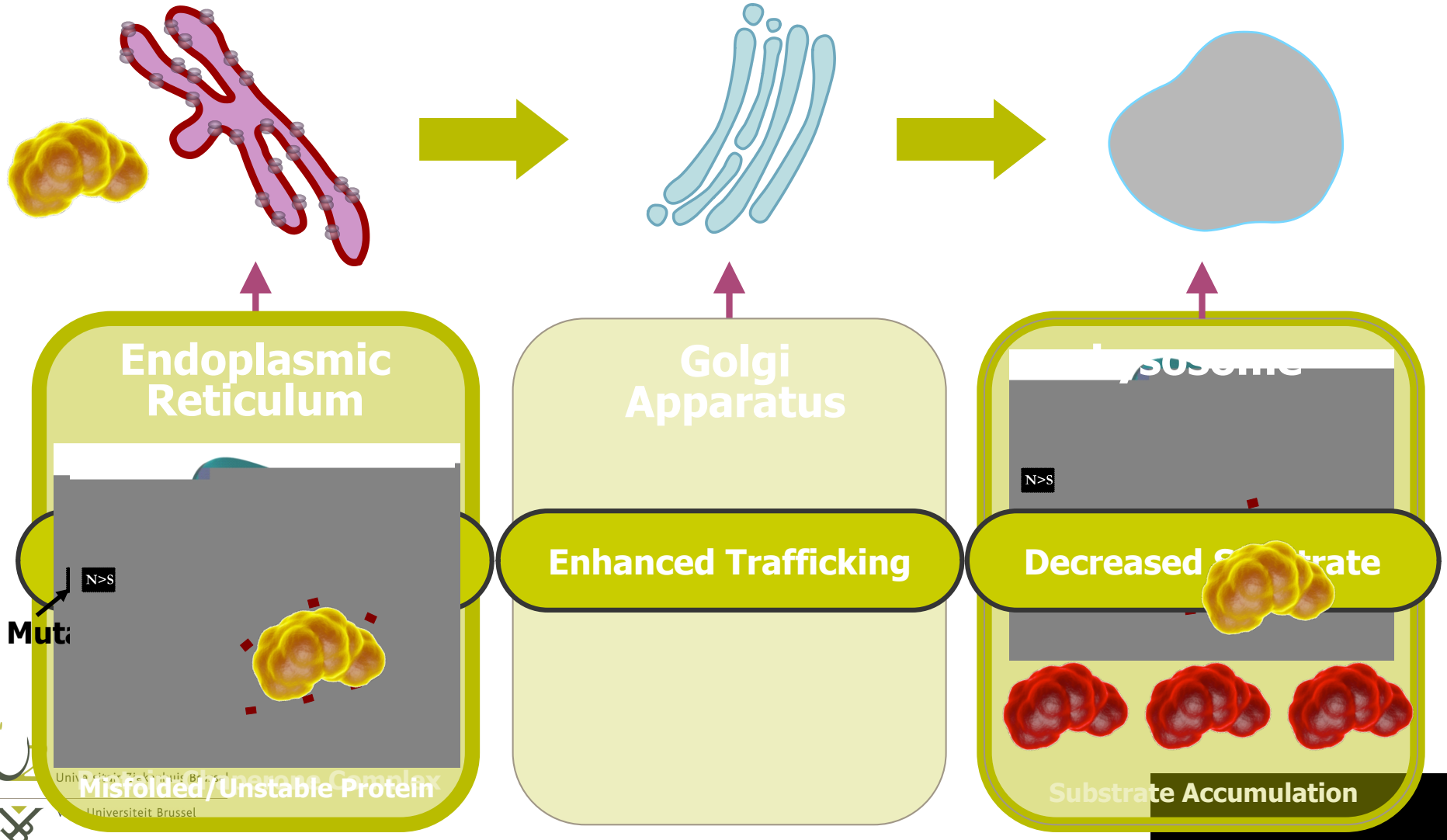
- In Fabry's disease degradation of lysosomal α galactosidase cause by some missense mutations in EPR as a result of misfolding
- Fabry, Gaucher, Tay-Sachs, Sandhoff, Pompe

- A number of substances in the different sphingolipid metabolism

GM1 gangliosidosis (Suzuki, 2007)

- A synthetic chaperone of b-galactosidase (NOEV) efficiently delivered to brain in mouse model and was able to increase enzyme levels in almost all areas of the brain
- N-octyl-4-epi-β-valienamine (NOEV) signifi-cantly increases the level of β-galactosidase in a transgenic (R201C) murine model and reduces level of GM1-ganglioside while also ameliorating the motor function of the mice when treatment is initiated at age 2 months but not later

Action of Chaperones

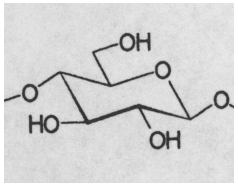


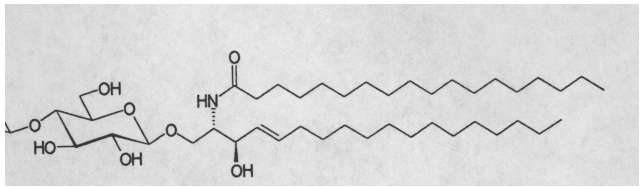
Substrate reduction

- reducing the amount of accumulating heparan sulfate
- Genistein inhibits GAG synthesis
- Miglustat in Gaucher disease

Glucosylceramide Degradation

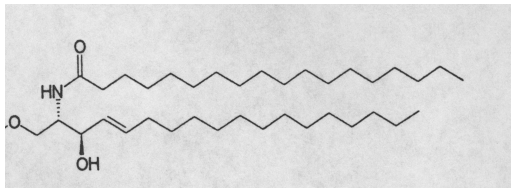
Glucose





Glucosylceramide

Glucocerebrosidase



Ceramide

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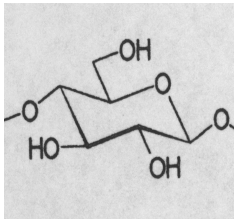
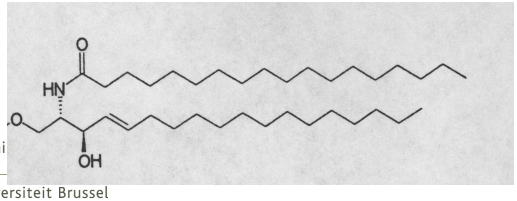
Synthesis of Glucosylceramide (Storage Compound in Gaucher Disease)

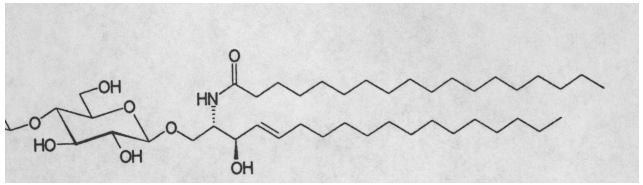
Glucose



Glucosylceramide-Synthase

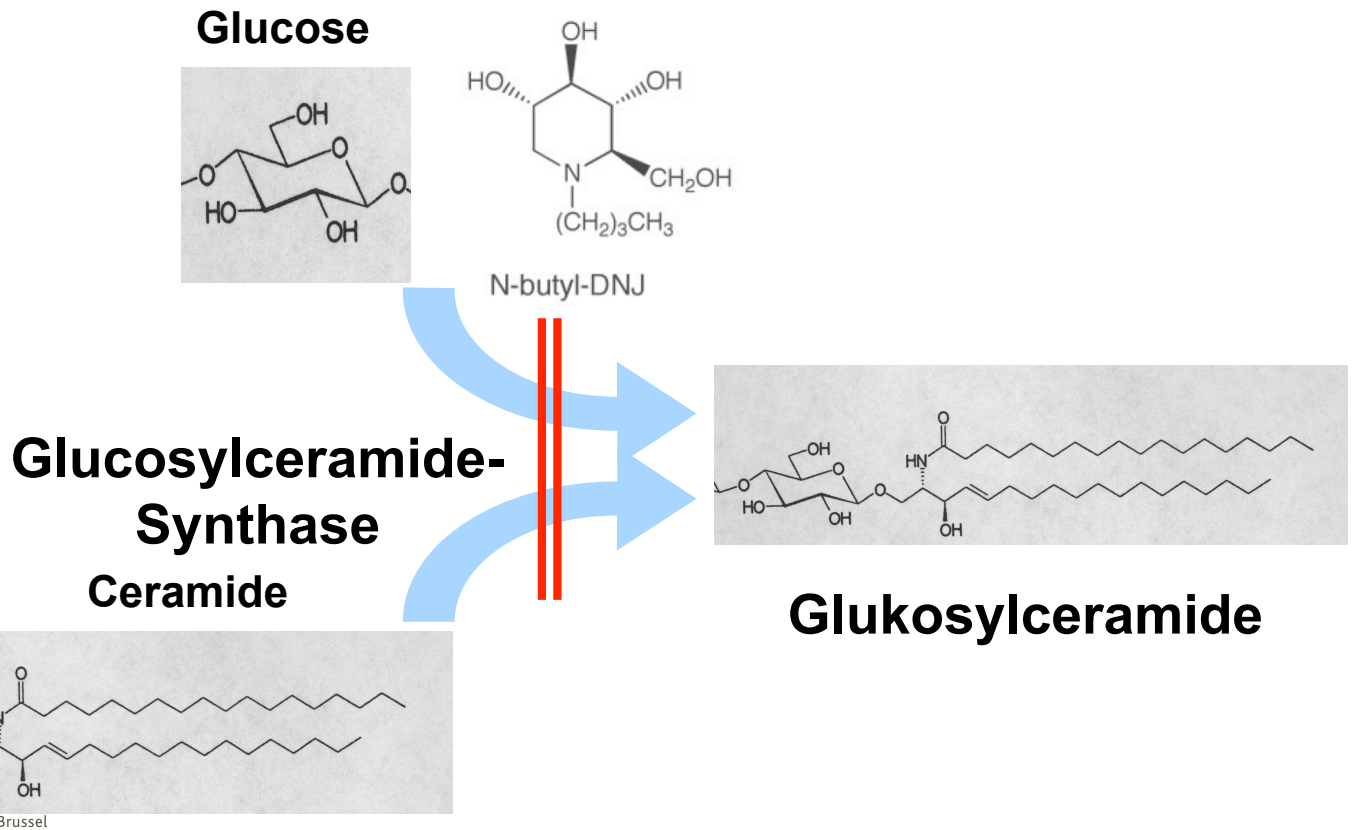
Ceramide



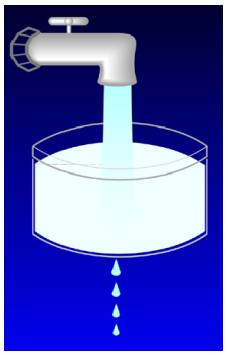


Glukosylceramide

Inhibition of Glucosylceramide Synthase

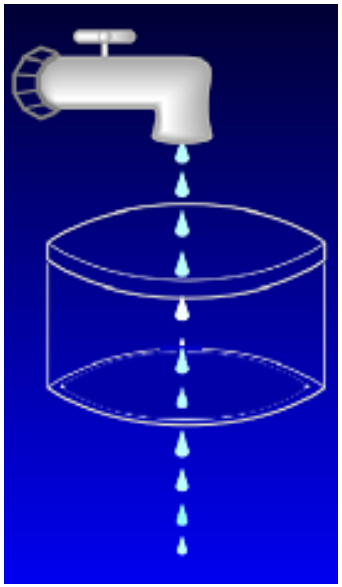


Enzyme Replacement (ERT)



Gaucher Disease

SI



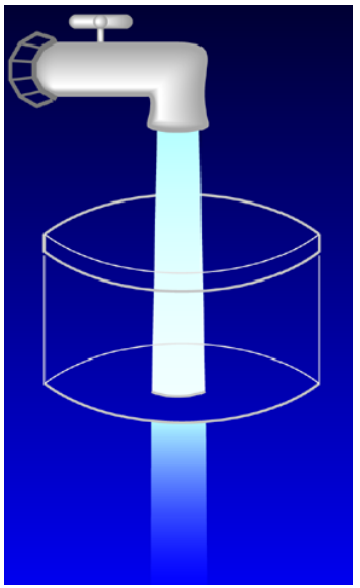
Glucose + Ceramide

↓

Glucosylzeramide

↓

Glucose + Ceramide



ERT

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Substrate Inhibition

- Advantages:
  - → Oral Application
  - → Passes the Blood-Brain-Barrier

- Disadvantages:
  - Diarrhoea
  - Weight loss
  - Neuropathy

- Genistein is a component (Isoflavone) of the Soya Bean
- In cultured skin cells fibroblasts Genistein blocks the glycosaminoglycan synthesis

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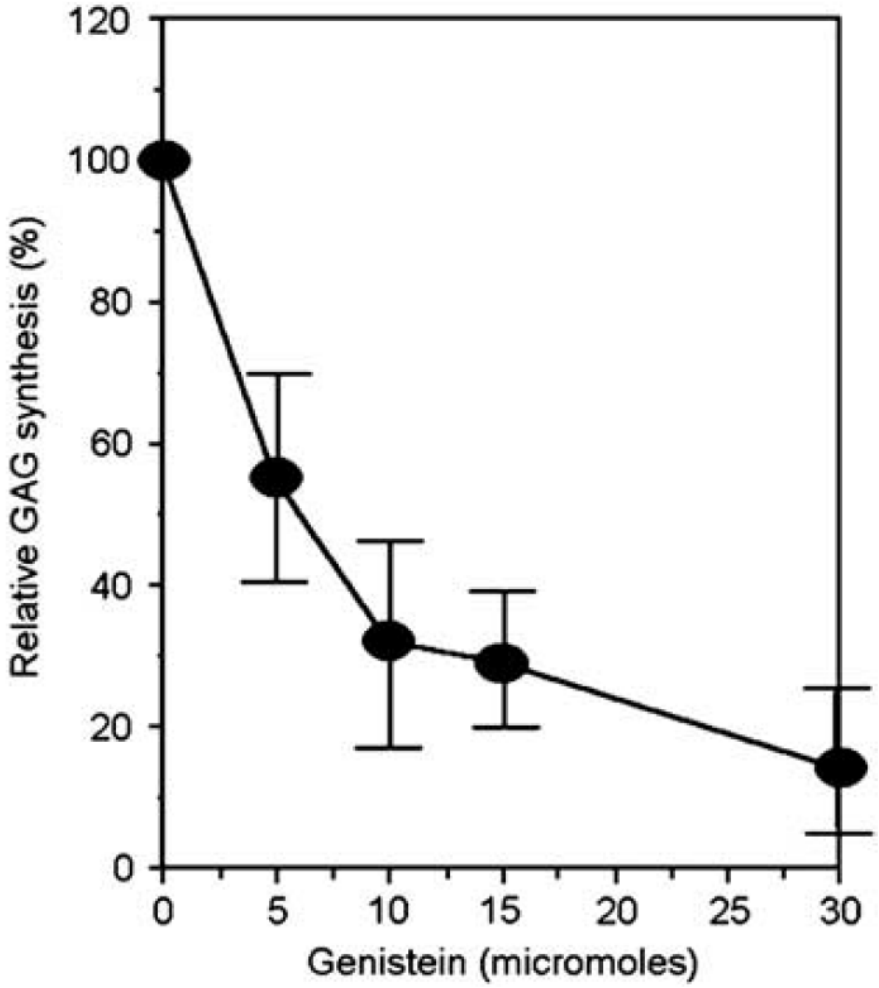
Effect of Genistein on GAG Synthesis in cultured Human Fibroblasts



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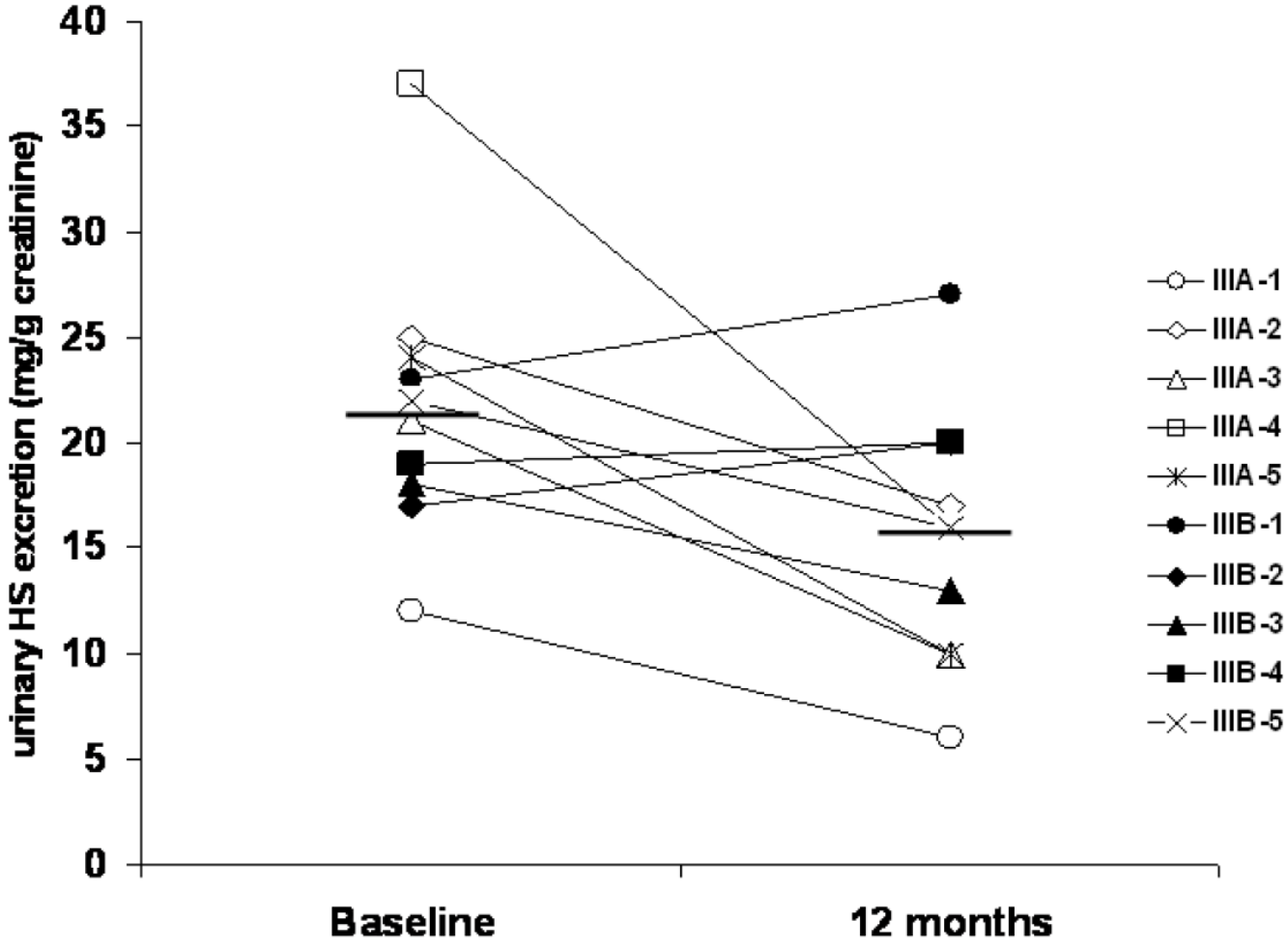
Piotrowska E et al (2006) *Eur J Hum Genet* **14**: 846

Effect of Genistein on GAG Excretion



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Piotrowska, E., et al., Current Therapeutic Research, 2008. **69**(2):166

GENISTEIN

- **Clinical efficac**

- **The next step: Animal studies**
  - **Dr. E. Wraith (England)**
  - **Dr. Scarpa (Italy)**

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