Creatine deficiency: clinical and therapeutic aspects

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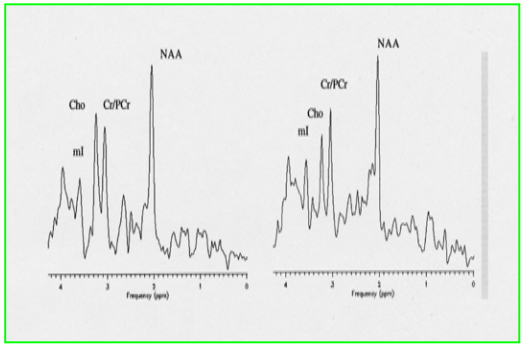
Milestones of Cr research



1835 discovery of Cr (Chevreul)

1927 discovery of PCr (Eggleton & Eggleton; Fiske & Subbarow)

1934 discovery of Cr reaction (Lohomann)

1981 PCr shuttle hypothesis (Bessman & Geiger)

1985 CK function (Tombes & Shapiro)

1993 CK knockout mice (van Deursen et al.)

1994 first case of GAMT deficiency (Stöckler et al.)

1996 three-dimensional structure of Mi-CK (Fritz-Wolf et al.)

2000-1 first case of AGAT deficiency (Bianchi et al., Item et al.)

2001 first case of CT1 deficiency (Cecil et al., Salomons et al.)

2001 GAMT knockout mice (Isbrandt et al.)

2004-6 AGAT deficiency phenotype is prevented by early treatment (Battini et al.)

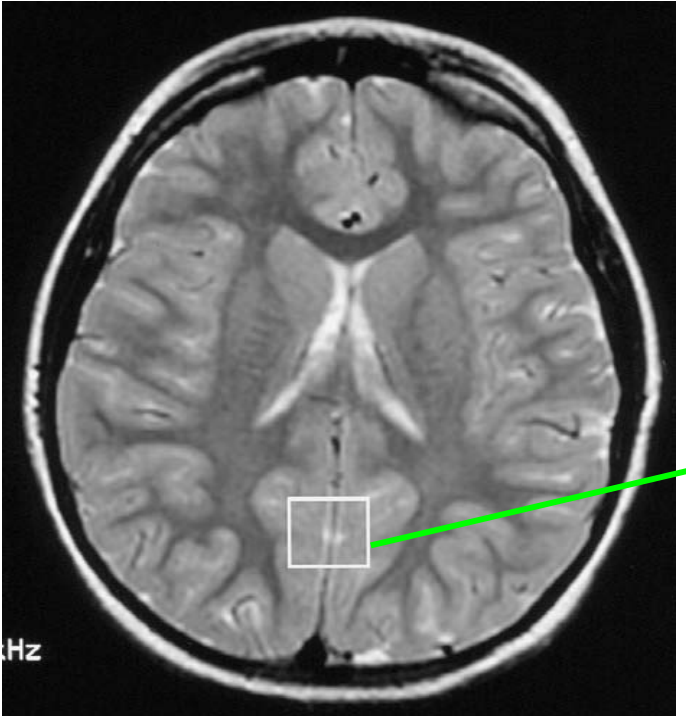
2005-7 GAMT deficiency phenotype is prevented by early treatment (Schulze et al.)

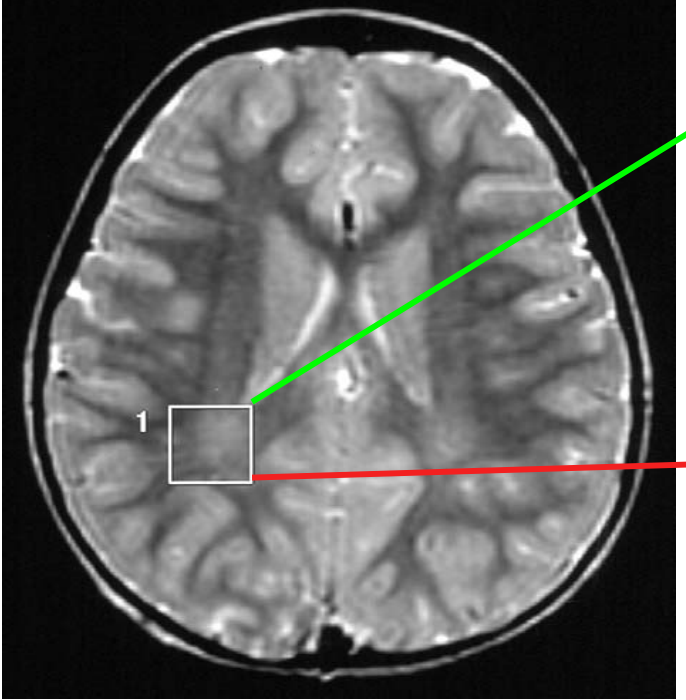
2007-8 Does Arg supplementation improve CT1 defect ?

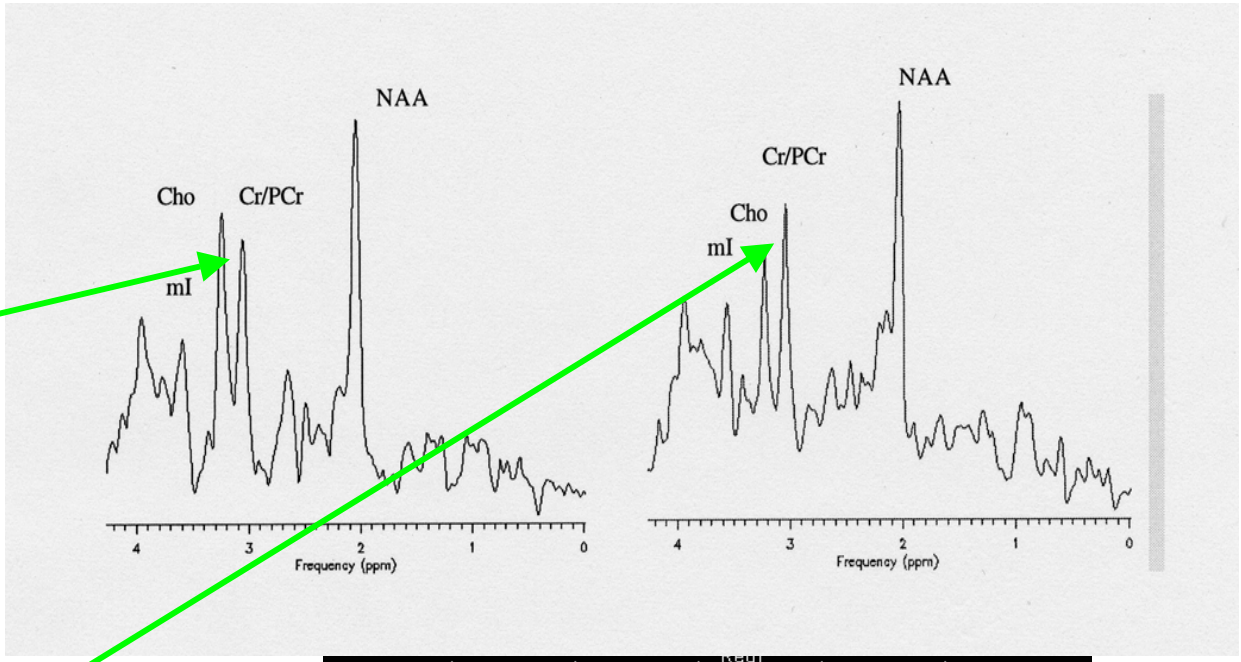
^{1}H-MRS, fortuity and *Cr disorder* discovery

- **"…Because the aforementioned results remained inconclusive, the patient …was investigated by magnetic resonance spectroscopy" (Stöckler et al., 1994)**
- **"…Despite these preliminary results, the girls underwent conventional MRI and ^{1}H-MRS scanning of the brain following our standard clinical protocol" (Bianchi et al., 2000)**
- **"…Head circumference increased from the 75th to the 95th percentile prompting MRI and proton MRS" (Cecil et al., 2001)**

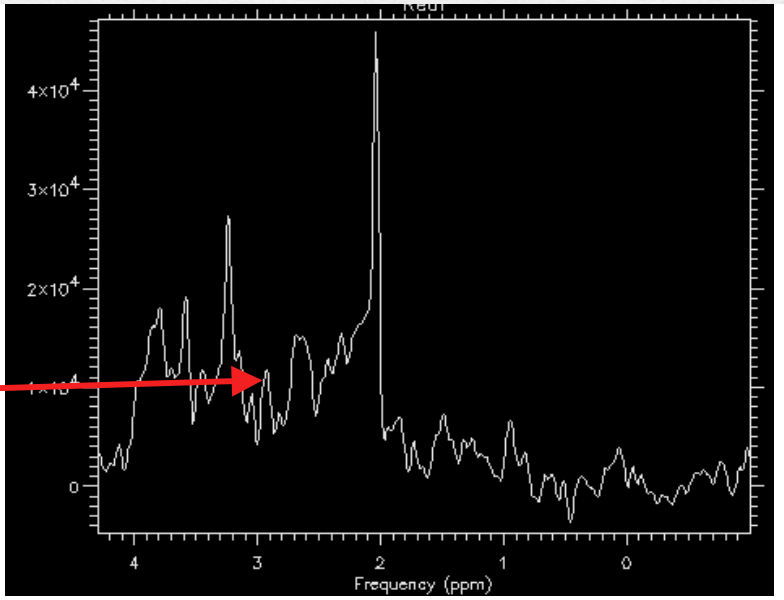
Brain ^{1}H-MRS







GAMTd



Cr synthesis

Urea cycle

gly

arg

AGAT

orn

gaa

S-adomet

Kidney

GAMT

S-adohcy

Liver

Cr

CT1

Muscle, Brain

ATP

ADP

Cr

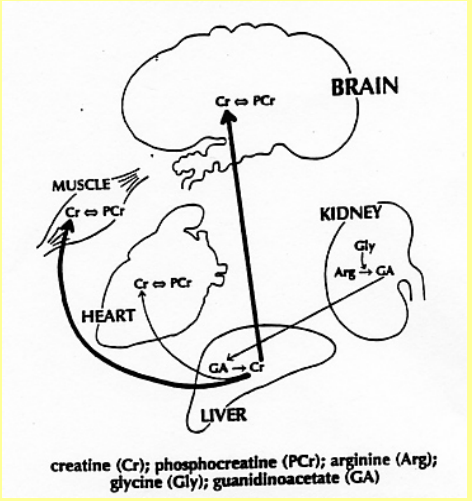
CK

PCr

Cr

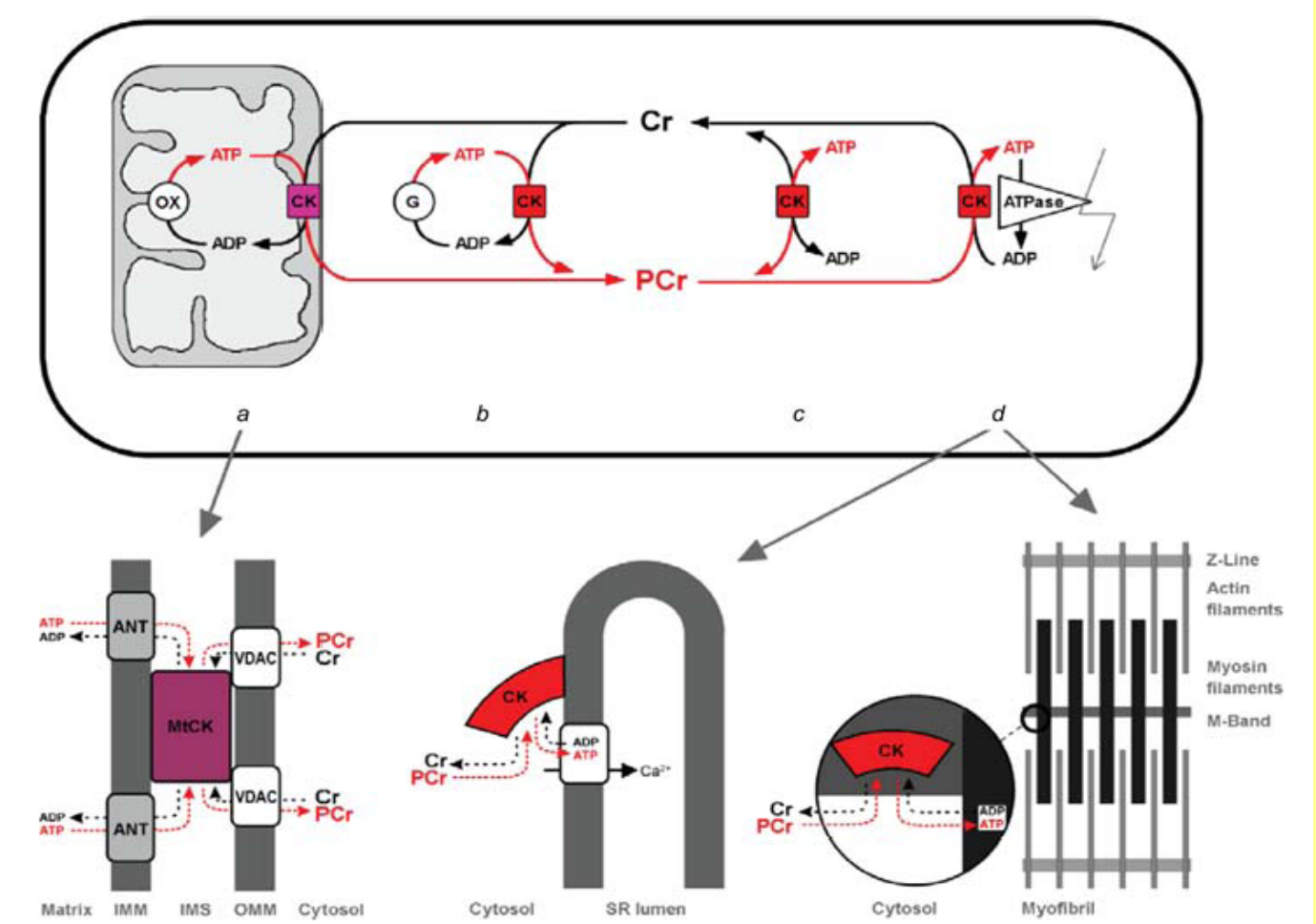
Crn

Urinary escretion



creatine (Cr); phosphocreatine (PCr); arginine (Arg); glycine (Gly); guanidinoacetate (GA)

The “shuttle” hypothesis and CK-PCr system



Saks et al., 2006

Genes involved in Cr metabolism

15q15.3 agat

DNA GENOMICO

cDNA

ORF 1269 bp

19p13.3 GAMT

DNA GENOMICO

cDNA

ORF 708 bp

Xq28 CT1

ATG

TGA

ORF 1905 bp

Tissue distribution of AGAT, GAMT, CT1, CK

Tissue/enzyme	AGAT	GAMT	CT1	CK
liver	+(+)	+++		
kidney	++	++	+	
pancreas	++	++		
lung	+	±		
heart/skeletal muscle	+	±	+	+
smooth muscle			+	
spleen	+	±		
brain	+	+	±	+
testis/ovary	+	++		+
timus	+			
retina				+
fibroblasts		±	+	

Questions

- **Does it exist a phenotypic pattern suggestive of Cr disorder syndrome(s) ?**
- **Is there a common clinical denominator for all Cr syndrome disorders**

The prevalence of inborn errors of Cr metabolism

- **GAMT deficiency**
  - **> 31 cases reported (5 Italian cases: 2 RM, 1 MI, 1 SI, 1 BA)**
  - **1/850 unexplained encephalopathies (1999-2003) (Leuzzi et al., 2005)**
- **CT1 defect**
  - **17 cases reported (Kleefstra et al., 2005)**
  - **6/288 (2.1%) families with XLMR (Rosemberg et al., 2004)**
  - **4(6)/478 (>1%) males with unexplained MR (Rosemberg et al., 2005)**
  - **~ 5 Italian patients (1 PI, 1 MI, 3 GE)**
- **AGAT deficiency**
  - **4+1 cases reported (2 families) (PI)**
  - **2 familial cases from Israel (Lisbon, 2008)**
  - **0/850 unexplained encephalopathies (1999-2003) (Leuzzi et al, 2005)**

AGAT

GAMT

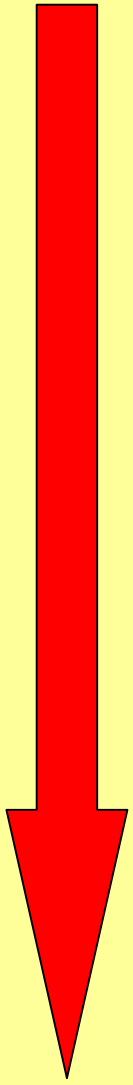
CT1

GAMT deficiency: the index case

(Stöckler et al., 1994)

- **22 month-old boy**
- **5 months:**
  - **developmental arrest → movement disorders**
- **22 months:**
  - **Severe hypotonia**
  - **Hemiballistic-dystonic dyskinesias**
  - **Brain MRI: bilateral abnormalities of globus pallidus**
  - **EEG: low background activity and multifocal spikes**

GAMT deficiency: Clinical findings

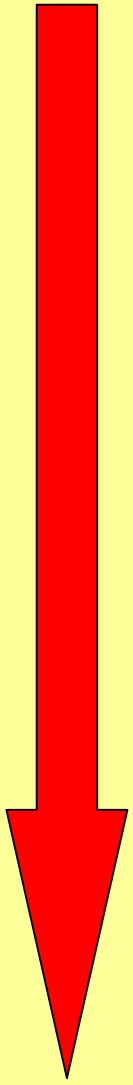


- Mental retardation and language disorder
- Epilepsy
- Autistic traits and other behavior disorders
- Hypotonia
- Myopathic muscle alterations
- Movement disorders and pallidum alterations (brain MRI)
- Late neurological deterioration
- Rare (?) symptoms: microcephaly (2) cirrhosis (1), failure to thrive

GAMT deficiency: onset

- **Age: 3-24 months (mainly 3-6 months)**
- **Symptoms:**
  - **Developmental arrest → neurological deterioration → seizures**
  - **Febrile convulsion → seizures → neurological deterioration**
  - **Psychomotor delay → transient regression during febrile illness (seizures)**
  - **Early derangement of communicative development → autistic behavior**

GAMT deficiency: Clinical findings



- Mental retardation and language disorder
- Epilepsy
- Autistic traits and other behavior disorders
- Hypotonia
- “Myopathic” muscle alterations
- Movement disorders and pallidum alterations (on brain MRI)
- Late neurological deterioration with (spastic) paraparesis, rigidity, ataxia

Mental retardation (27/27)

Mercimek-Mahmutoglu et al, 2007

Progressive psychomotor delay

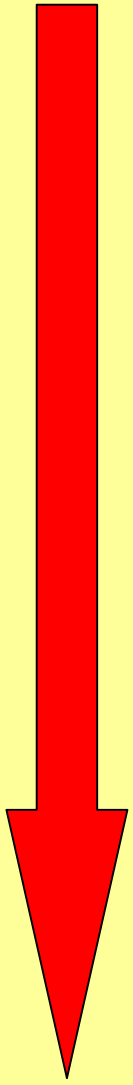
No language development

Behavior disorders: autistic spectrum, hyperactivity, aggressiveness, selfish injurious conducts

Definitive mental retardation:

- **Severe (21/27)**
- **Moderate (3/27)**
- **Mild (3/27)**

GAMT deficiency: Clinical findings



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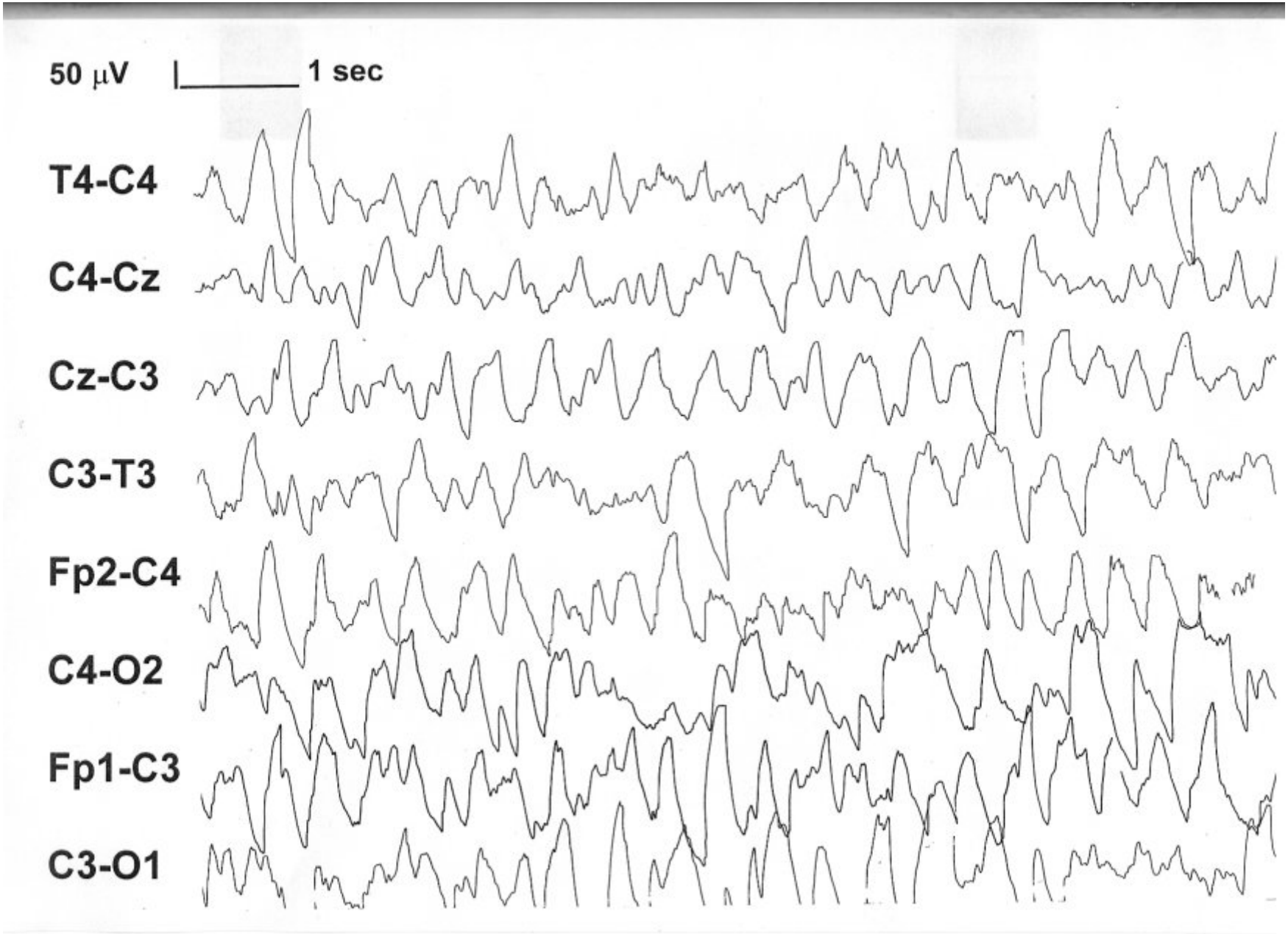
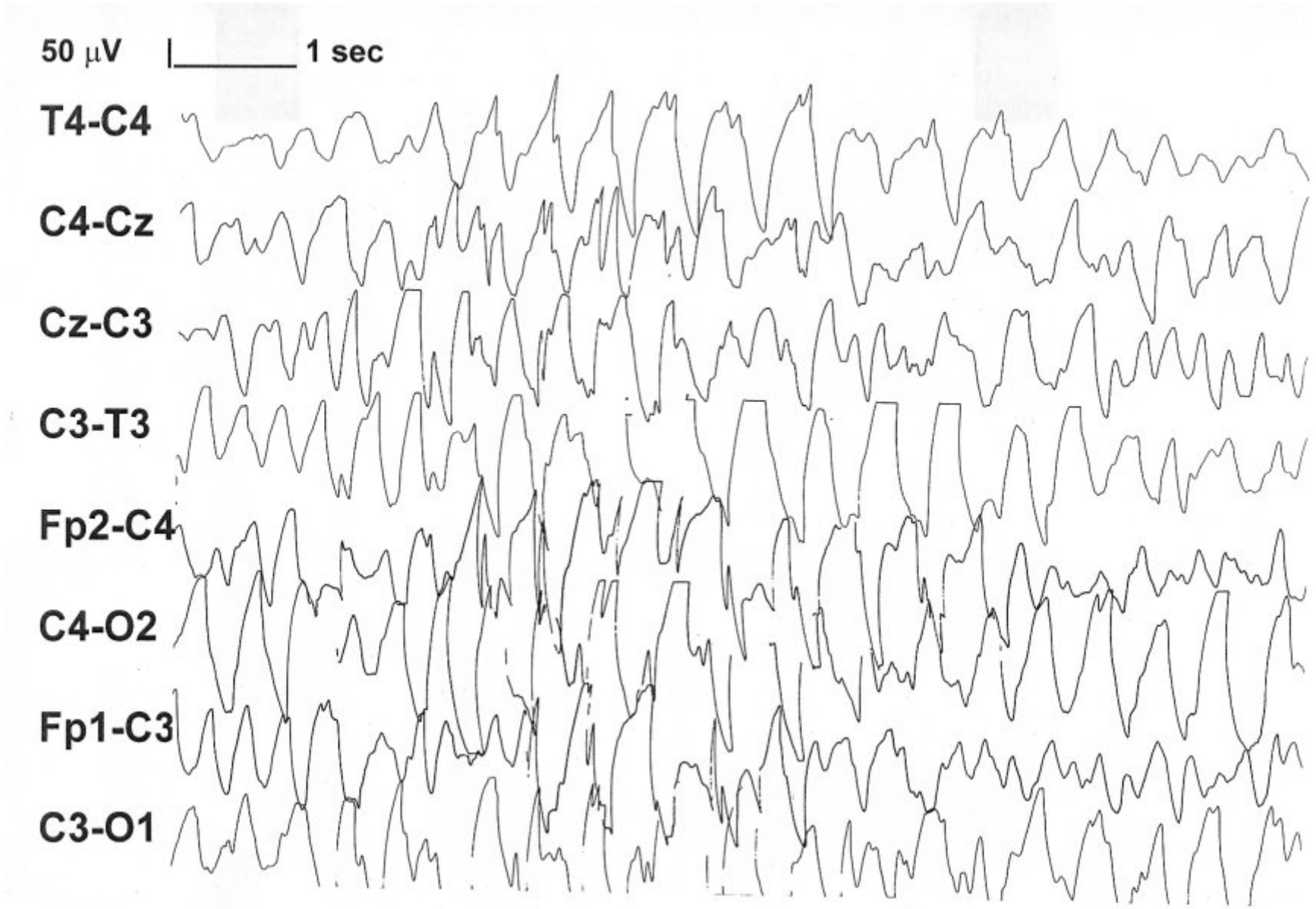
Epilepsy (25/27)

(Mercimek-Mahmutoglu et al, 2007)

- Variable pattern of seizures in the same patient
- Type of seizures:
  - generalized tonic-clonic seizures,
  - drop attacks,
  - absences,
  - life-threatening tonic seizures with apnea,
  - absences with myoclonic seizures,
  - partial seizures with secondary generalization
- EEG: bilateral or multifocal spikes and slow wave discharges
- Drug-responsive epilepsy (18/25)
- Drug unresponsive epilepsy (7/25)



Interictal EEG



Ictal EEG

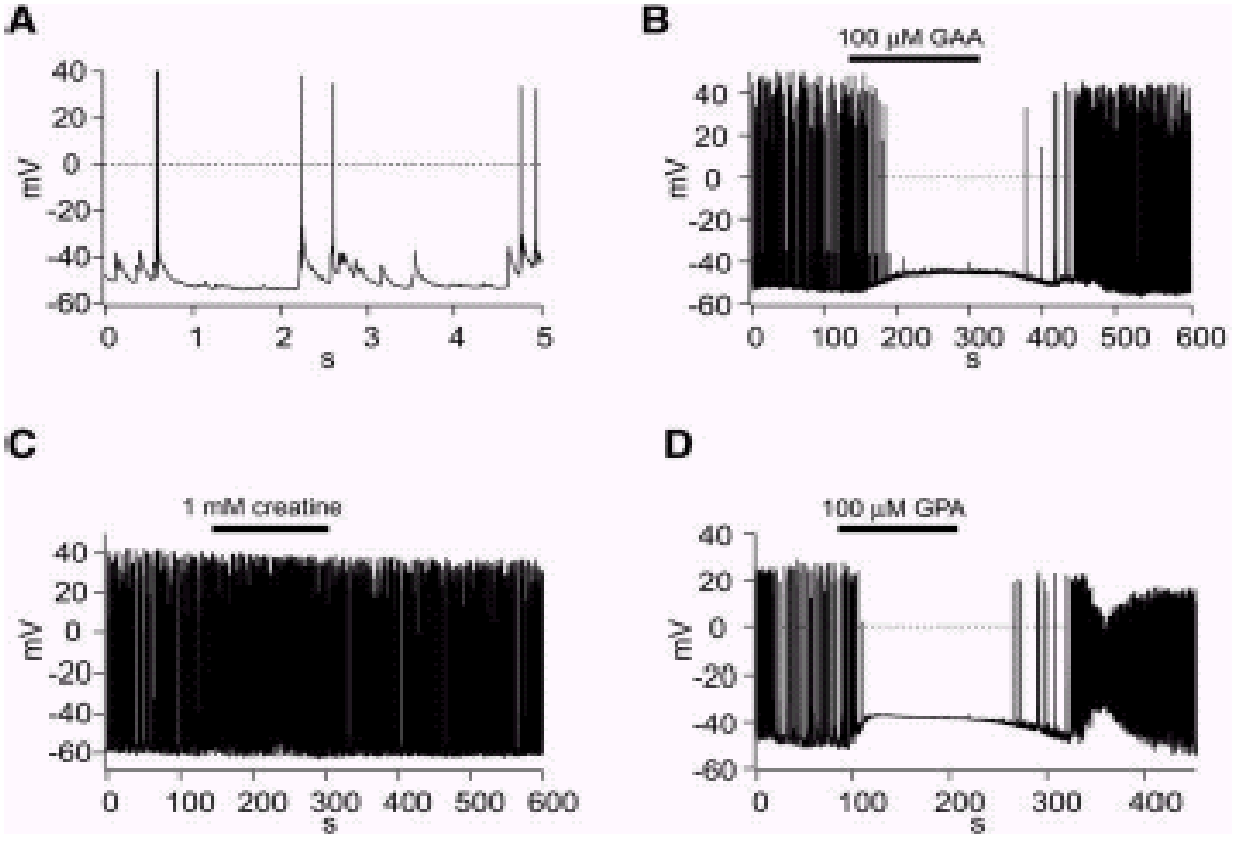
GAA in *GAMT deficiency*: hypotheses

- **Desensitization of $GABA_A$ receptors** → increase of neuronal excitability
- **Antagonizing action**: reduction of maximal $GABA_A$ receptor activation
- **Anionic gradient shift**: during prolonged activation of $GABA_A$ receptors the postsynaptic membrane response change from hyper- to depolarization (Staley and Proctor, 1999)

GAA and $GABA_A$ receptors

Neu et al., 2002

$GABA_A$ Receptor Activation by Guanidinoacetate

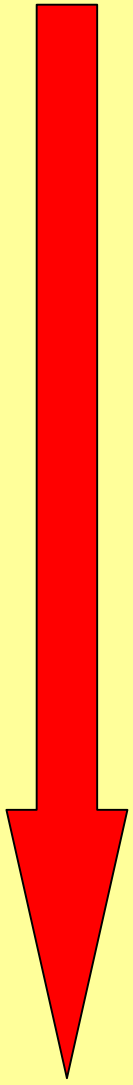


Neurotoxicology of guanidino compounds (GC)

- **GC could induce convulsions when administered to rabbits intracisternally**
- **GC generate peroxide radicals → peroxidation of polynsaturated fatty acids**
- **GAA activates chloride channels on neuronal $GABA_A$ neurons**
- **GAA acts on GP and cortex neurons through activation of $GABA_A$ receptors**
- **GAA is weak GABA-mimetic and acts as a direct $GABA_A$ agonist**

(Mori, 1987; Neu et al, 2002)

GAMT deficiency: Clinical findings



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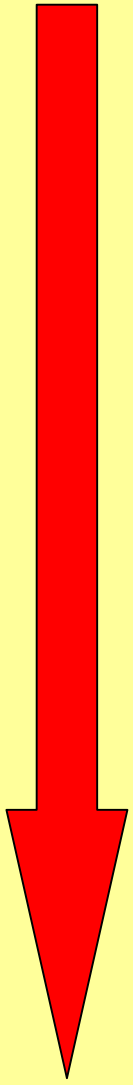
Hypotonia and myopathic muscle alterations

- **Hypotonia (8/24)** **(Mercimek-Mahmutoglu et al, 2007)**
- **"Myopathy"** **(Vilarinho et al, 2004)**
- **De Vries et al (2005):**
  - **18 year-old boy**
  - **epilepsy, psychomotor delay, failure to thrive → dyskinesias, behavior disorder**
  - **↑ serum alanine, ↑ urine ethylmalonic acid**
  - **Muscle biopsy: normal oxidation rate and single enzyme activities, ↓ ATP production**

GAMT deficiency: Clinical findings



Mental retardation and language disorder

Epilepsy

Autistic traits and other behavior disorder

Hypotonia

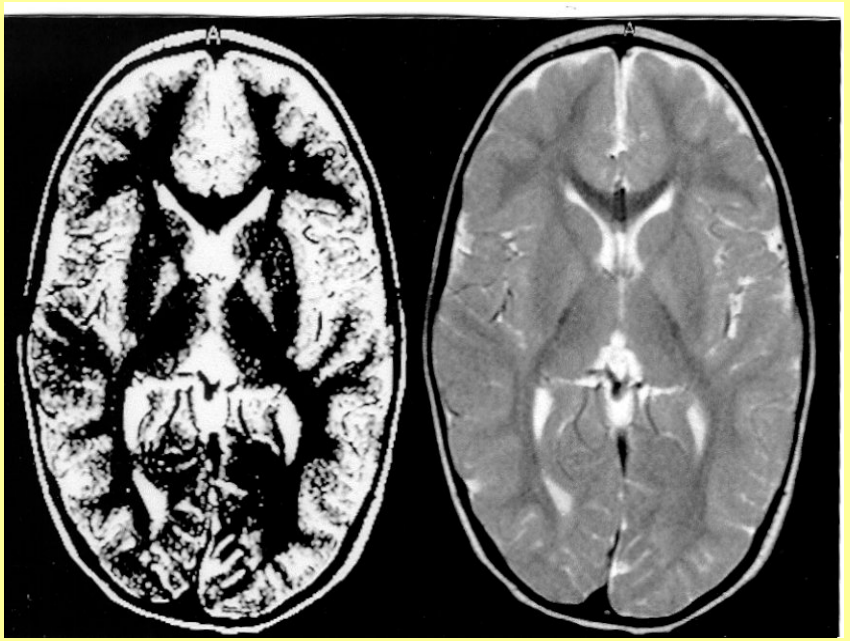
Myopathic muscle alterations

Movement disorders and pallidum alterations (on brain MRI)

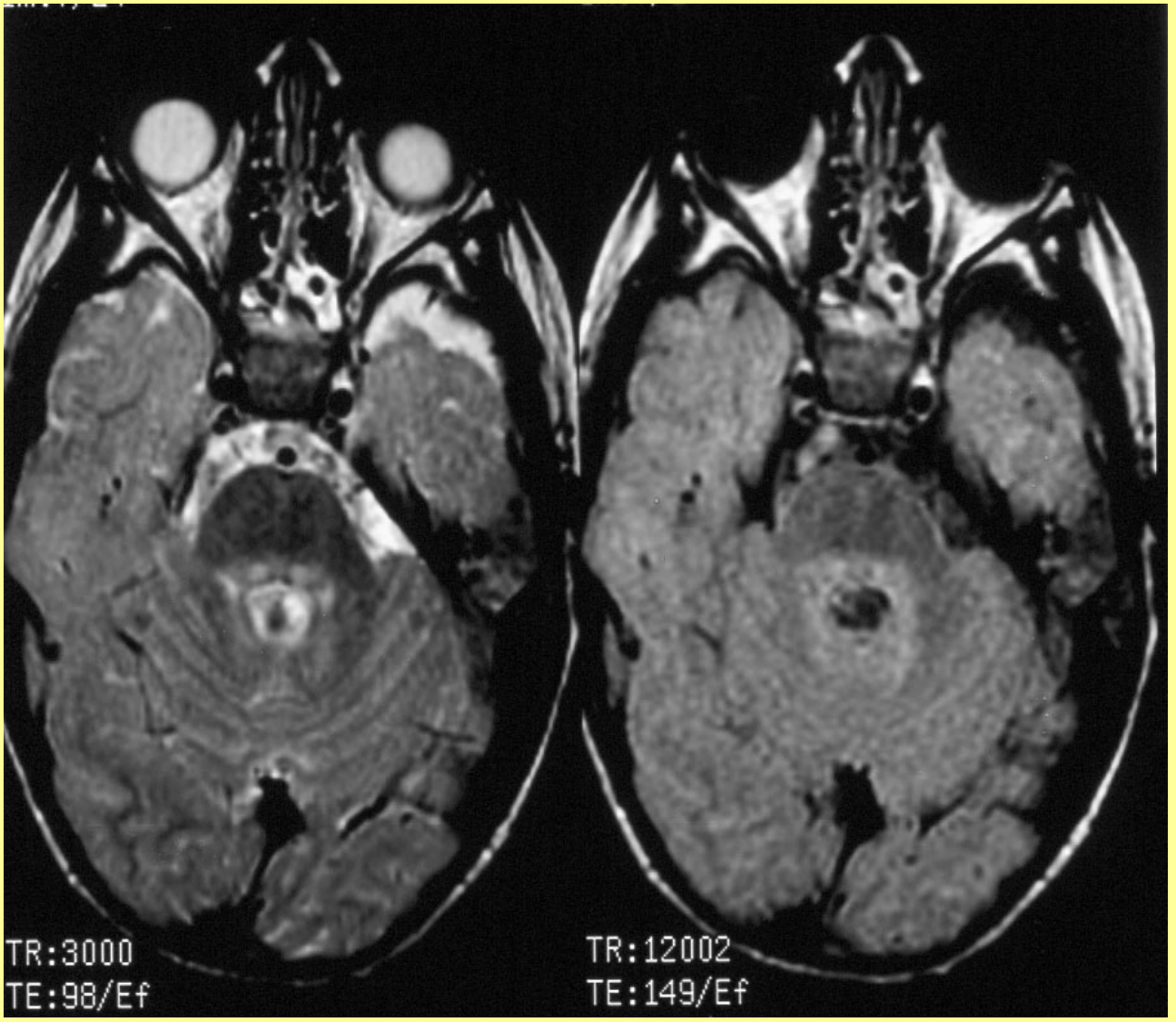
Late neurological deterioration

Movement disorders and pallidum alterations (brain MRI)

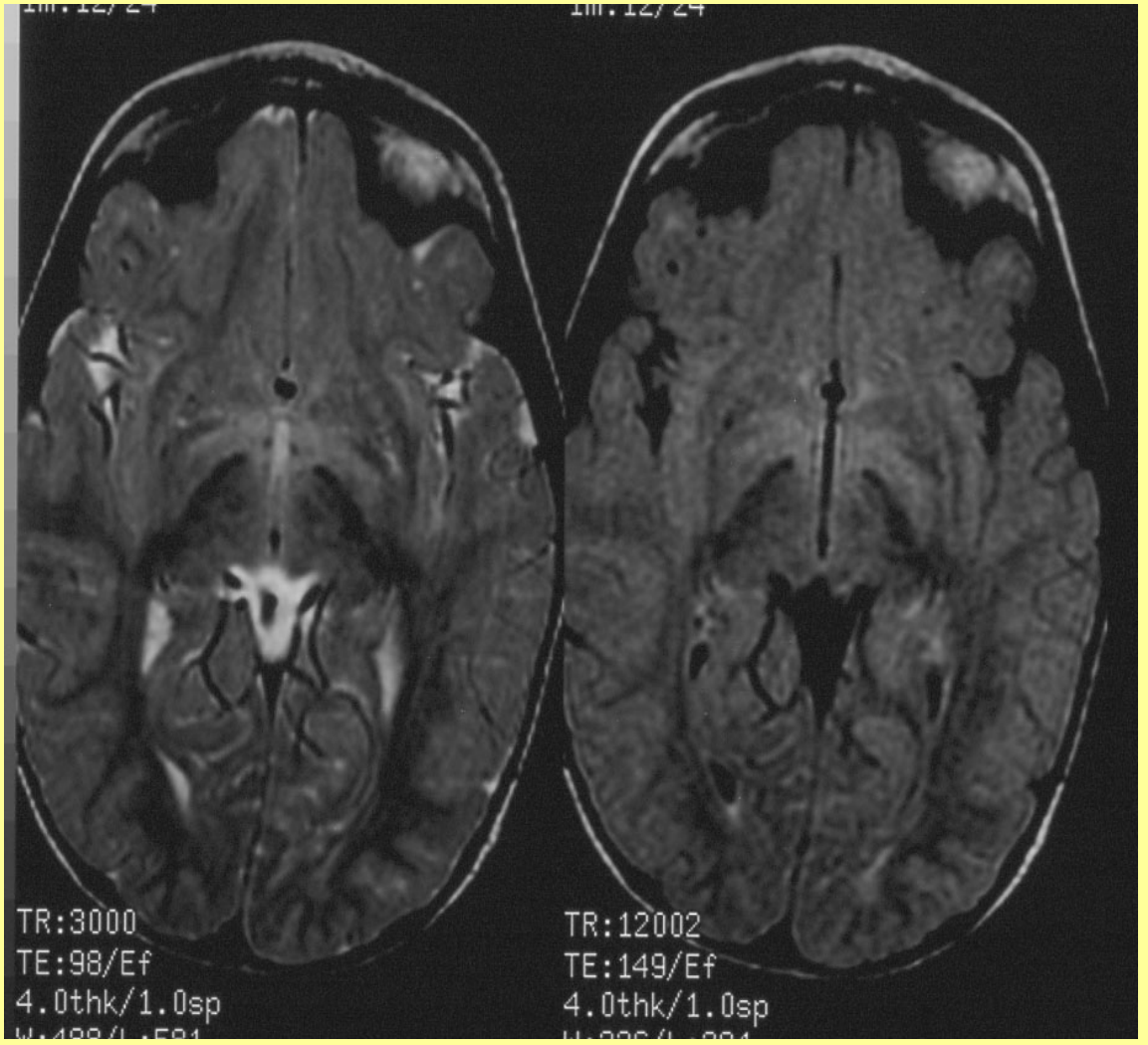
- **Athetosis, chorea, choreoathetosis, ballismus, dystonia (13/27)**
- **Pallidum alteration (6/22) associated (4) or not (2) with md**



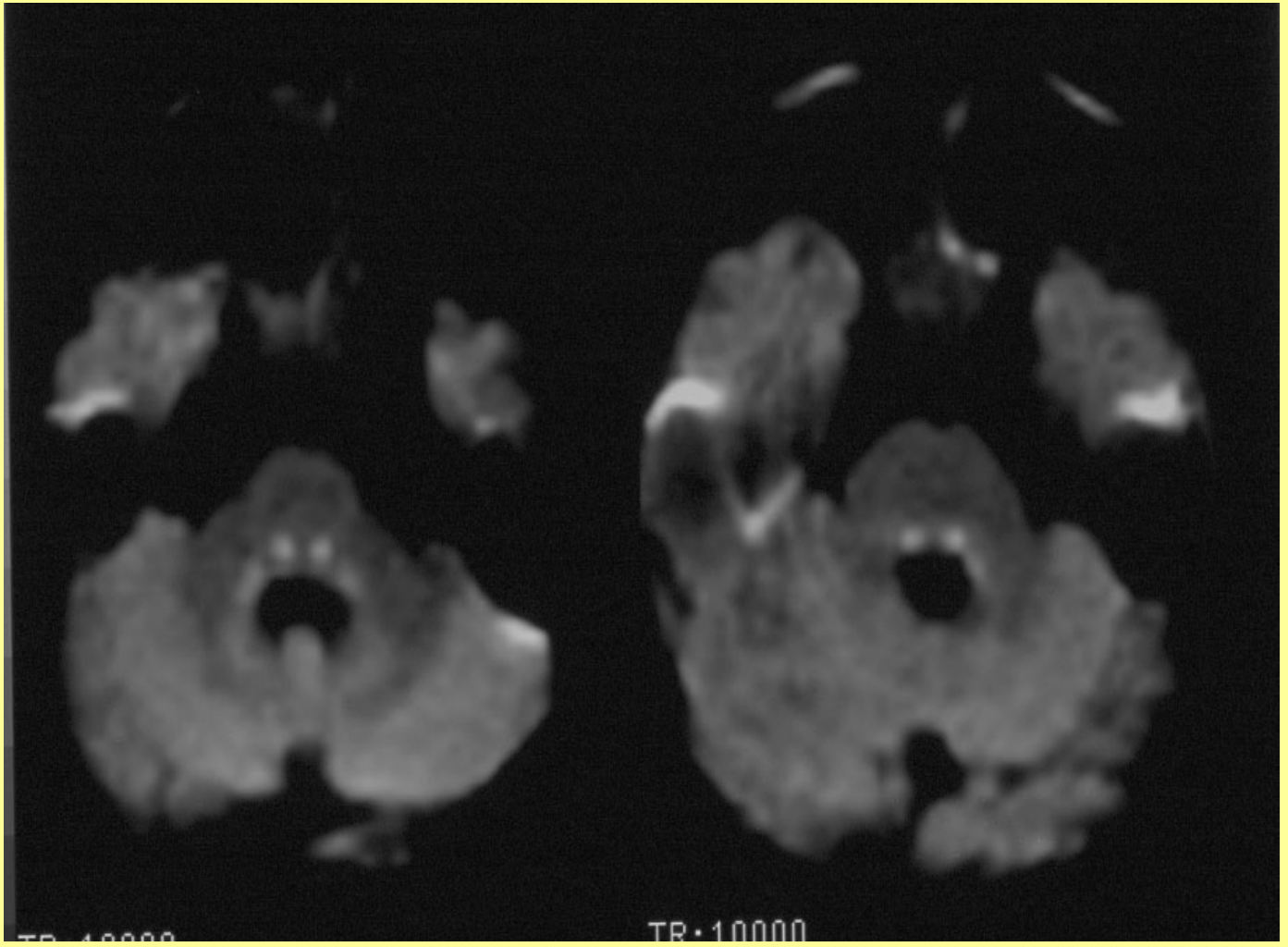
Mercimek-Mahmutoglu et al, 2007



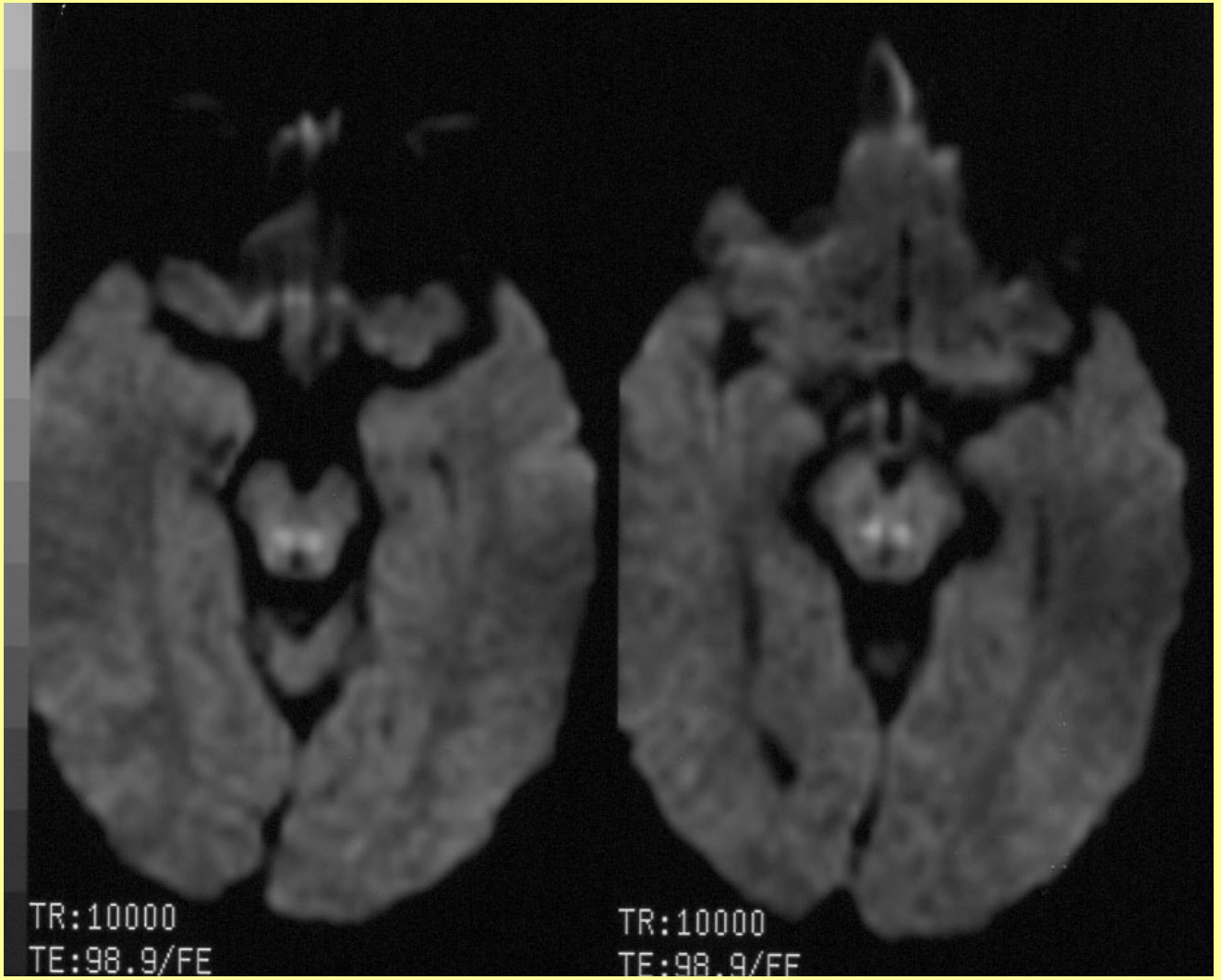
P.L. 3 yrs, T2/FLAIR images



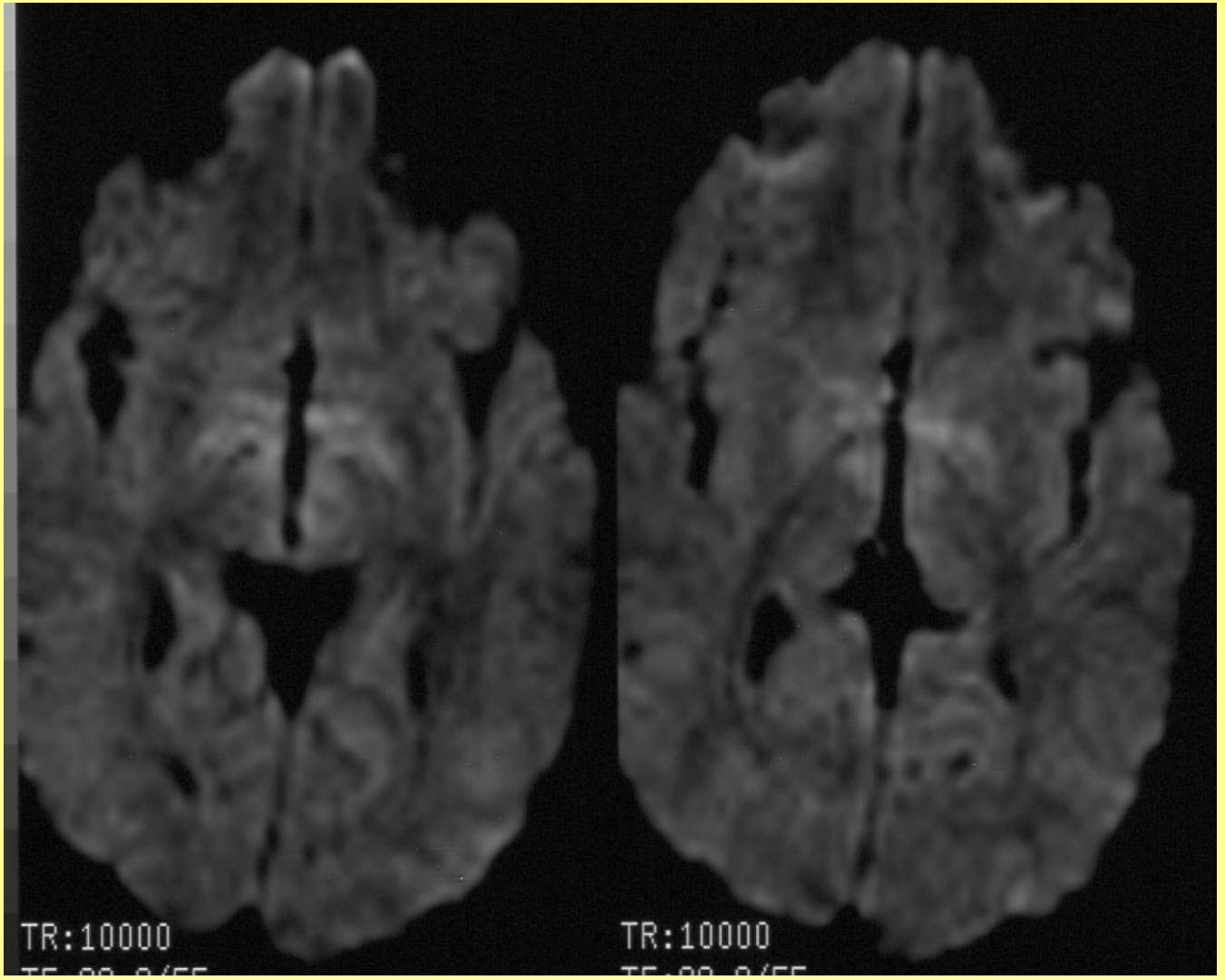
P.L. 3 yrs, T2/FLAIR images



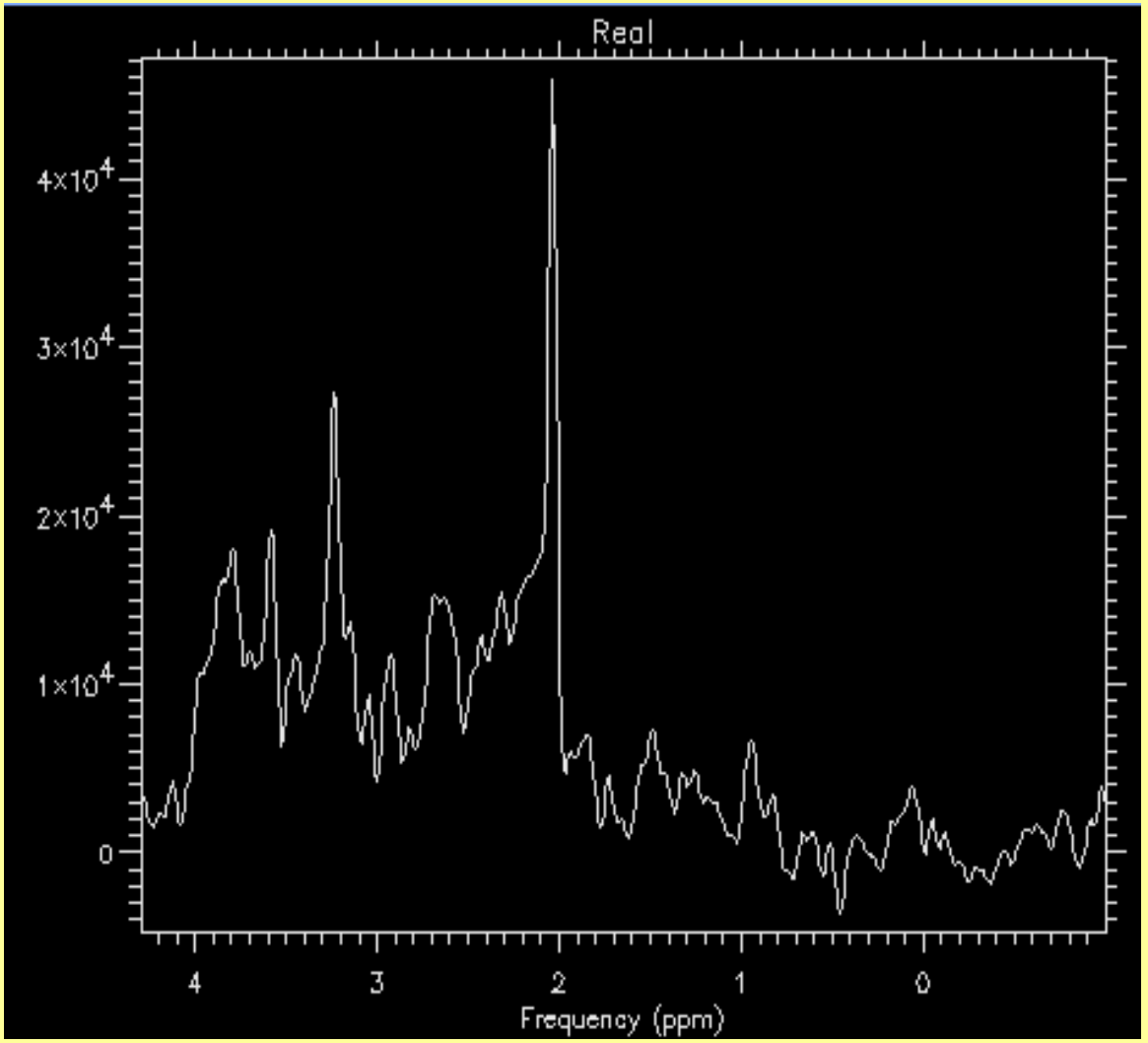
P.L. 3 yrs DWI



P.L. 3 yrs DWI

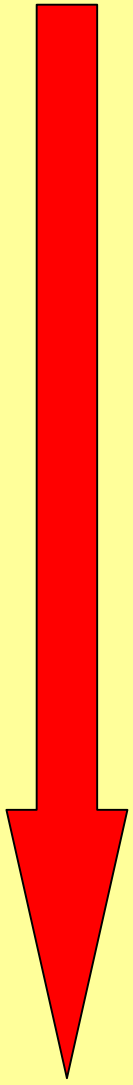


P.L. 3 yrs DWI



P.L. ^{1}H-MRS at diagnosis

GAMT deficiency: Clinical findings



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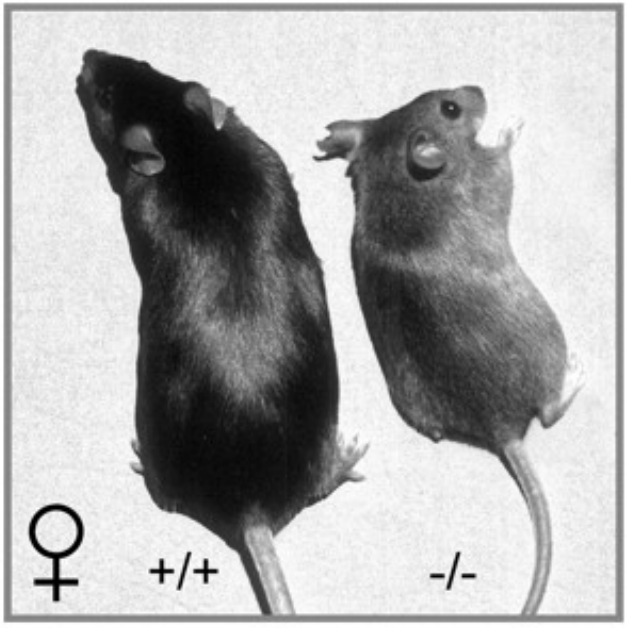
Is GAMT deficiency a progressive disorder ?

- *Caldeira Araujo et al. (2005):*
  - case 1 and 2 (26, 29 yrs) → late onset paraparesis and rigidity
  - case 3 → dead (22 yrs)
  - case 5 (19 yrs) → hypertonia and rigidity

GAMT $^{-/-}$ mouse phenotype



Schmidt et al, 2004; Torremans et al, 2005; Kan et al, 2005

- No severe neurological symptoms
- Mild cognitive defect (impaired retrieval of learned information)
- Muscular hypotonia
- ↓Maximal tetanic and twitch force
- ↓ relative force
- ↑ Relaxation times
- ↓↓ early force production during high-intensity fatigue
- Reduced body mass (F>M)
- Increased neonatal mortality
- Decreased male fertility

Cr synthesis

Urea cycle

gly

arg

AGAT

orn

gaa

S-adomet

Kidney

GAMT

S-adohcy

Liver

Cr

CT1

Muscle, Brain

ATP

ADP

Cr

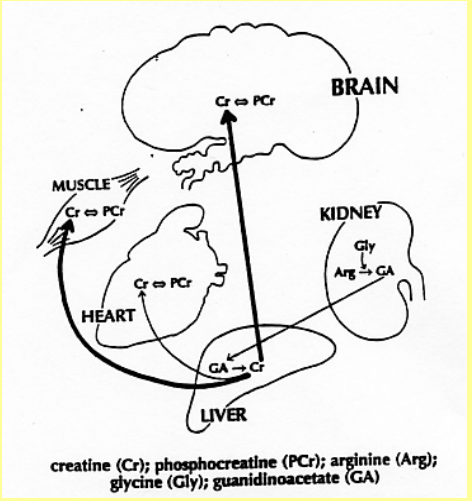
CK

PCr

Cr

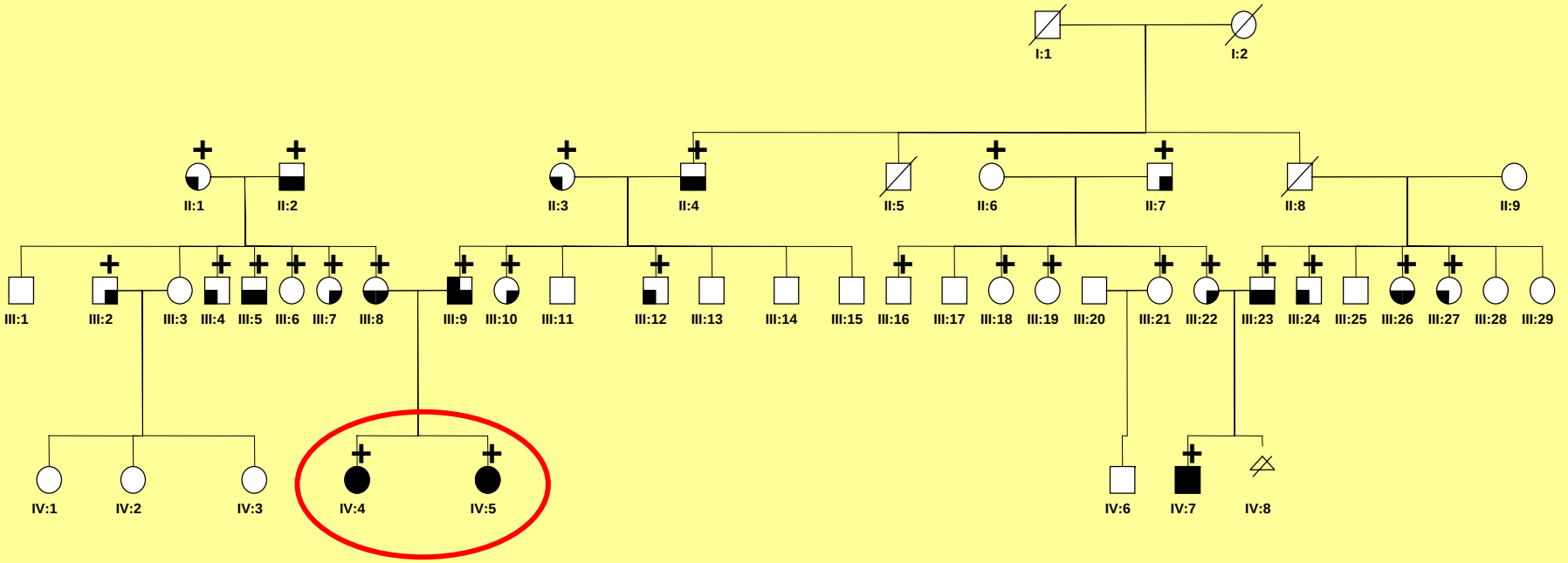
Crn

Urinary escretion



creatine (Cr); phosphocreatine (PCr); arginine (Arg); glycine (Gly); guanidinoacetate (GA)

AGAT deficiency

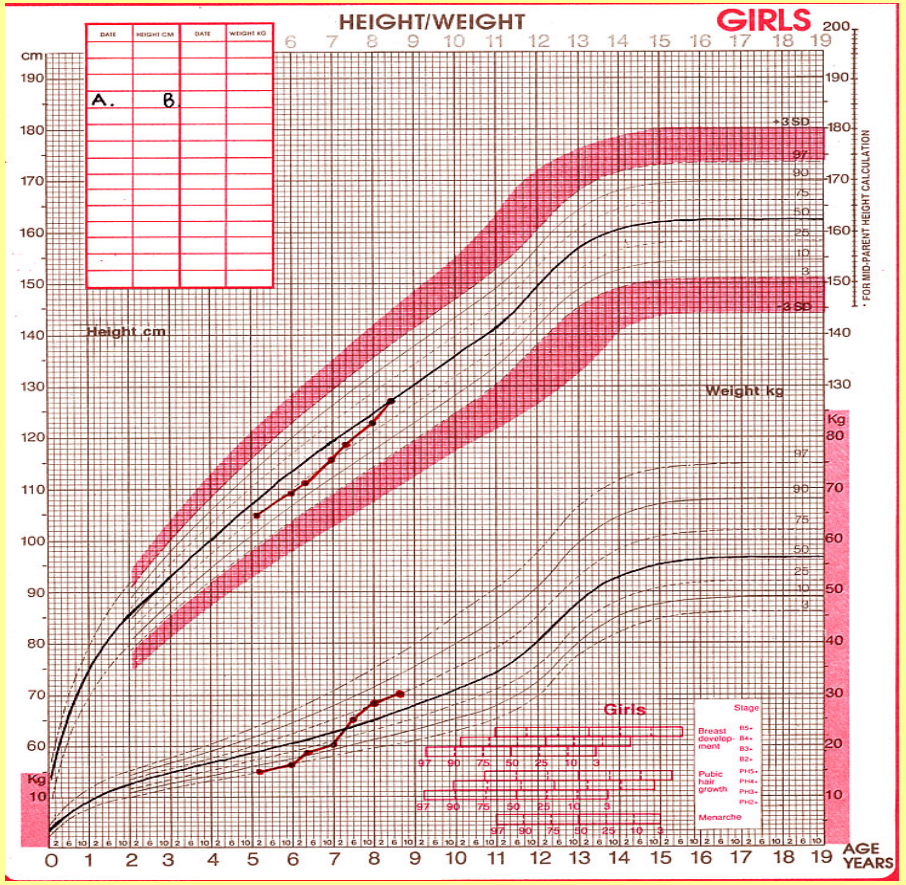


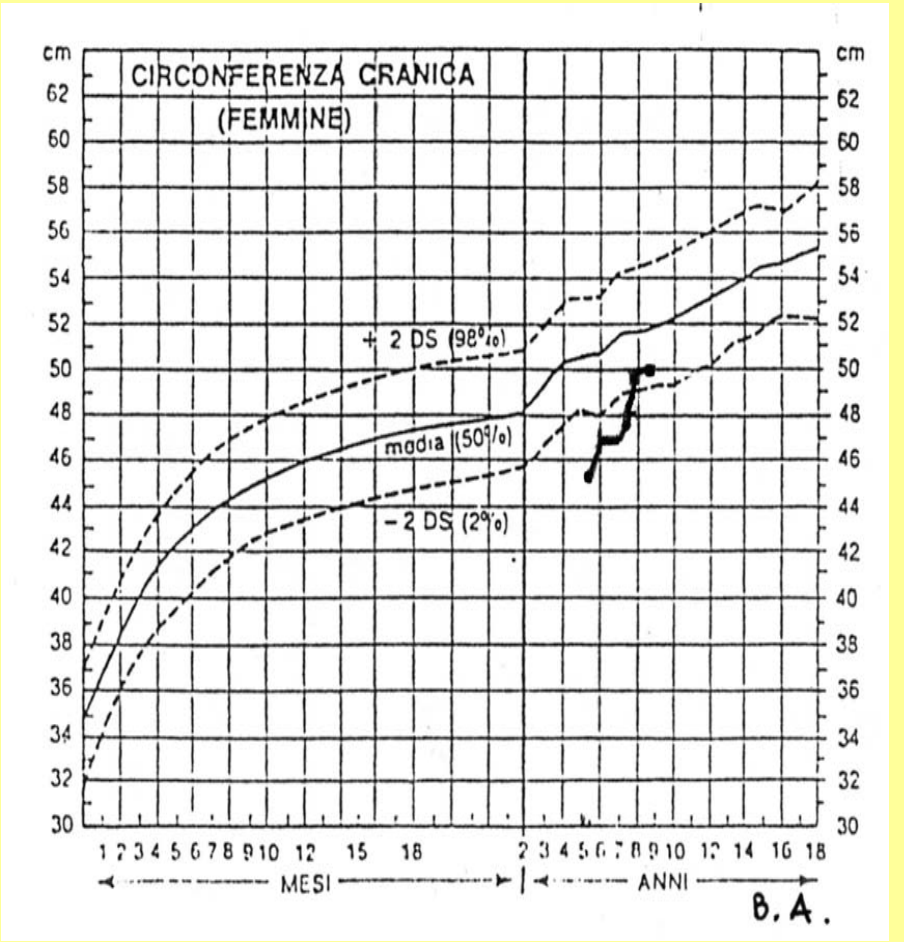
Bianchi et al, 2000, Item et al, 2001, Battini et al. 2002

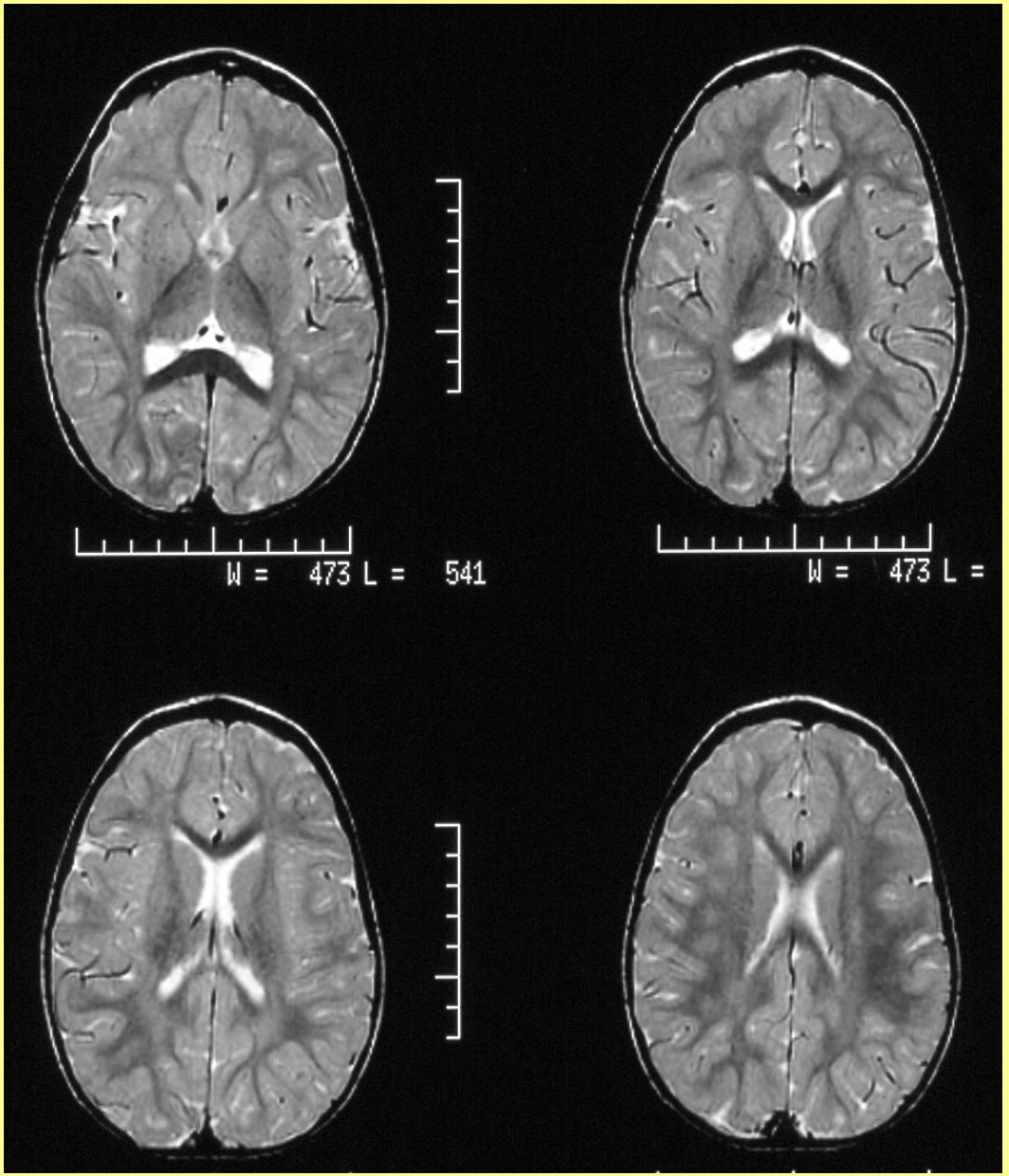
AGAT deficiency: phenotype

- **Psychomotor delay (walking unaided: 24 mo, first words: 30 mo)**
- **Hypotonia (mild)**
- **Secondary microcephaly**
- **Weight < 2SD**
- **Mental retardation (mild to moderate at performance tests)**
- **Absence of language**
- **Mild behavioral disorder (poor social contact, short attention span, stereotyped movements of the hands)**

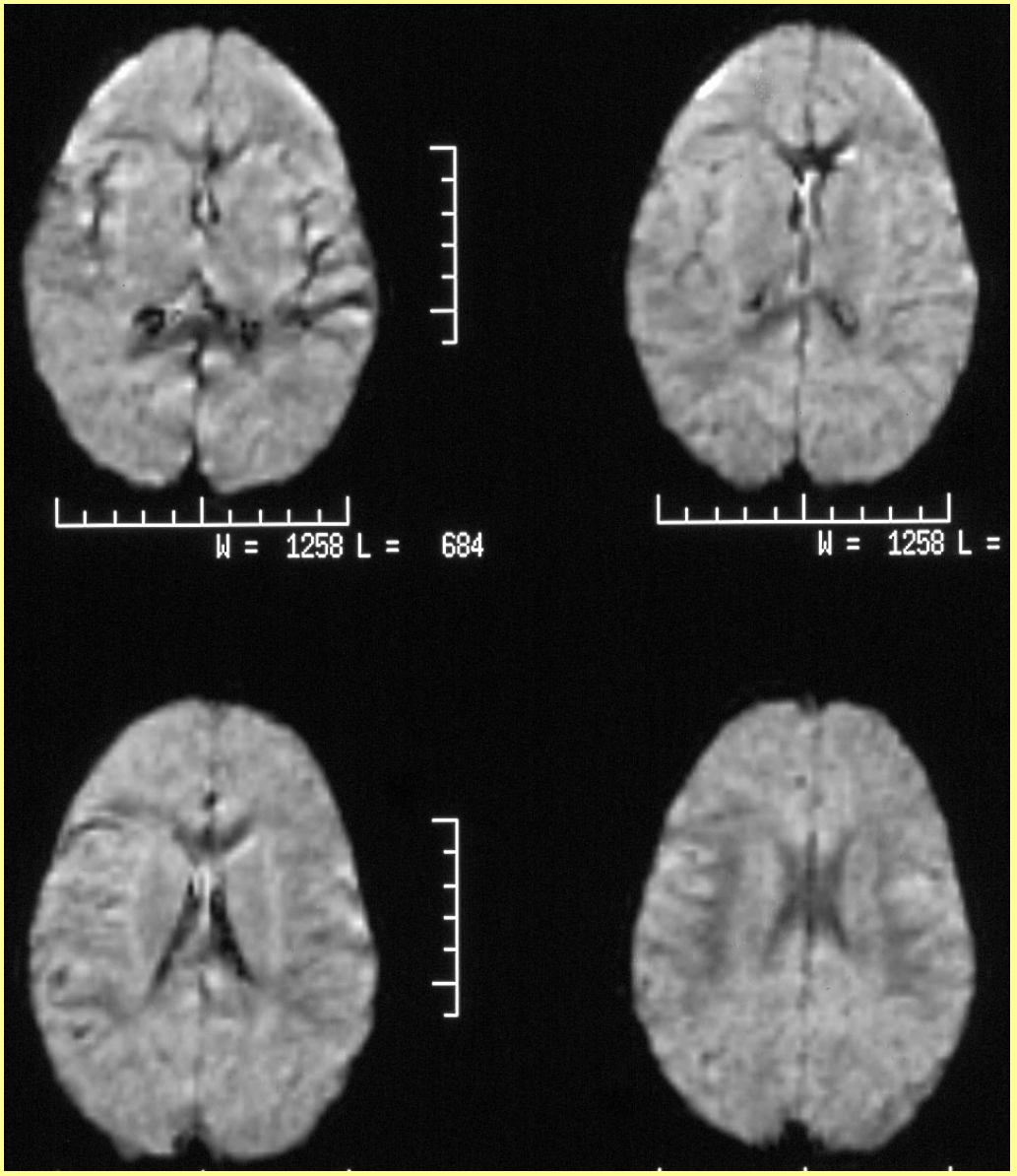
AGAT deficiency: somatic growth







A. G.S. 2 yrs.



A. G.S., DWI

Creatine deficiency: clinical and therapeutic aspects

Cr metabolism: quantitative aspects

- > 90% of total bodily Cr is in the muscle tissue, ~ 1.5% in the CNS
- Cr biosynthesis accounts for ~ 70% of the total utilization of labile methyl groups in the body
- Cr biosynthesis accounts for ~ 50% of the total Cr pool
- 1.7%/day of total Cr pool (~2g/day) is converted non-enzymaticaly into Crn
- Arg is the limiting amino acid in Cr synthesis
- Cr homeostasis requires about 2.3 g Arg/day (50% of daily intake of Arg)
- % of Arg in CNS ?
- % of CNS Arg for Cr synthesis ?

Cr synthesis

Urea cycle

gly

arg

AGAT

orn

gaa

S-adomet

Kidney

GAMT

S-adohcy

Liver

Cr

CT1

Muscle, Brain

ATP

ADP

Cr

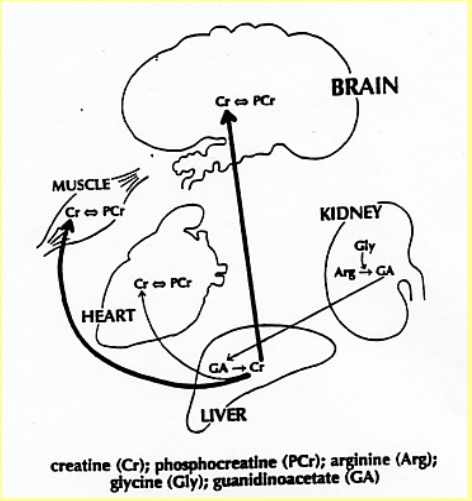
CK

PCr

Cr

Crn

Urinary escretion



creatine (Cr); phosphocreatine (PCr); arginine (Arg); glycine (Gly); guanidinoacetate (GA)

The treatment of Cr defects

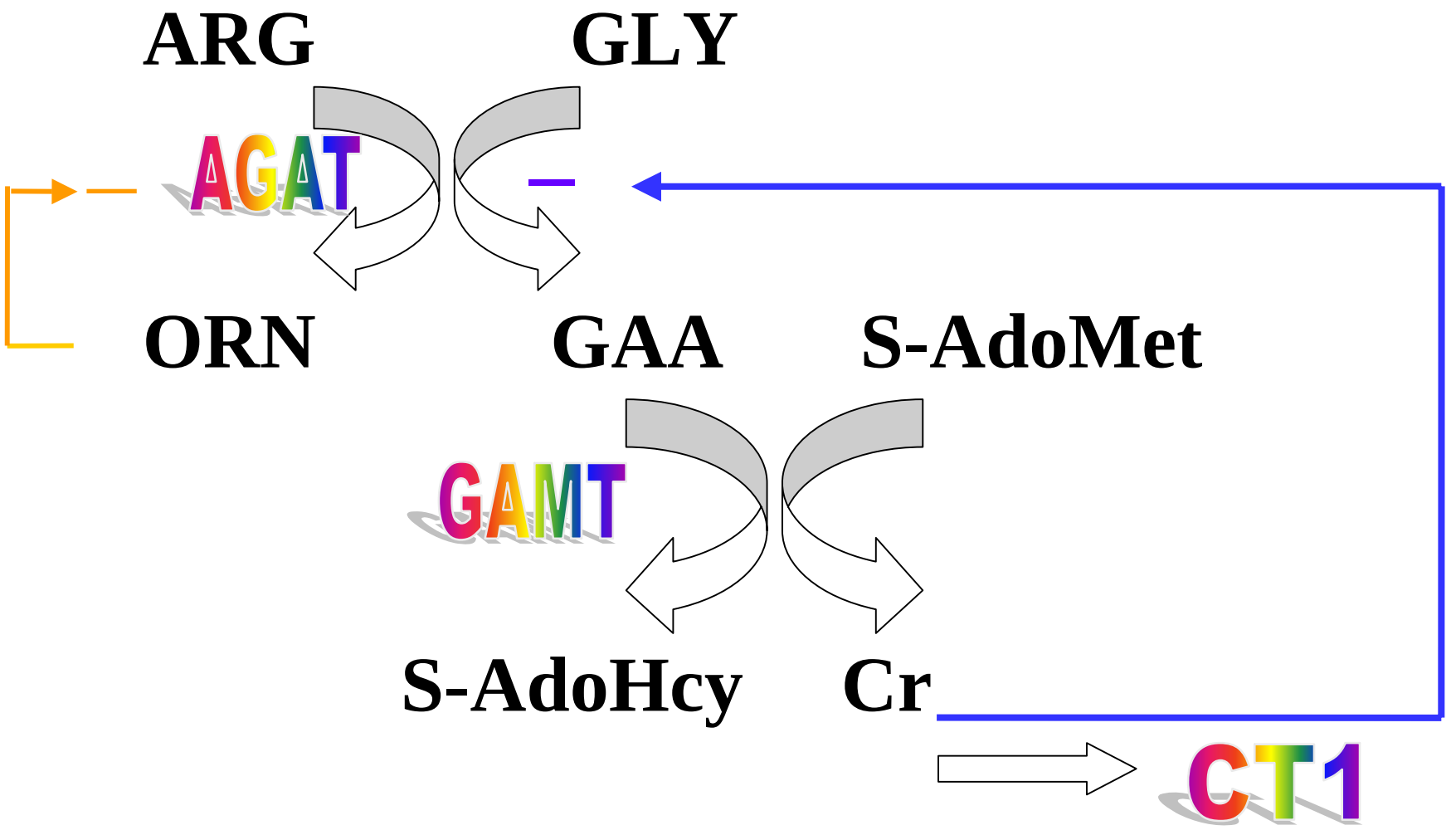
Targets

- **GAMT deficiency:**
  - **1) reintegration of brain Cr pool**
  - **2) reduction of GAA accumulation**
- **AGAT and CT1 defects:**
  - **reintegration of brain Cr pool**

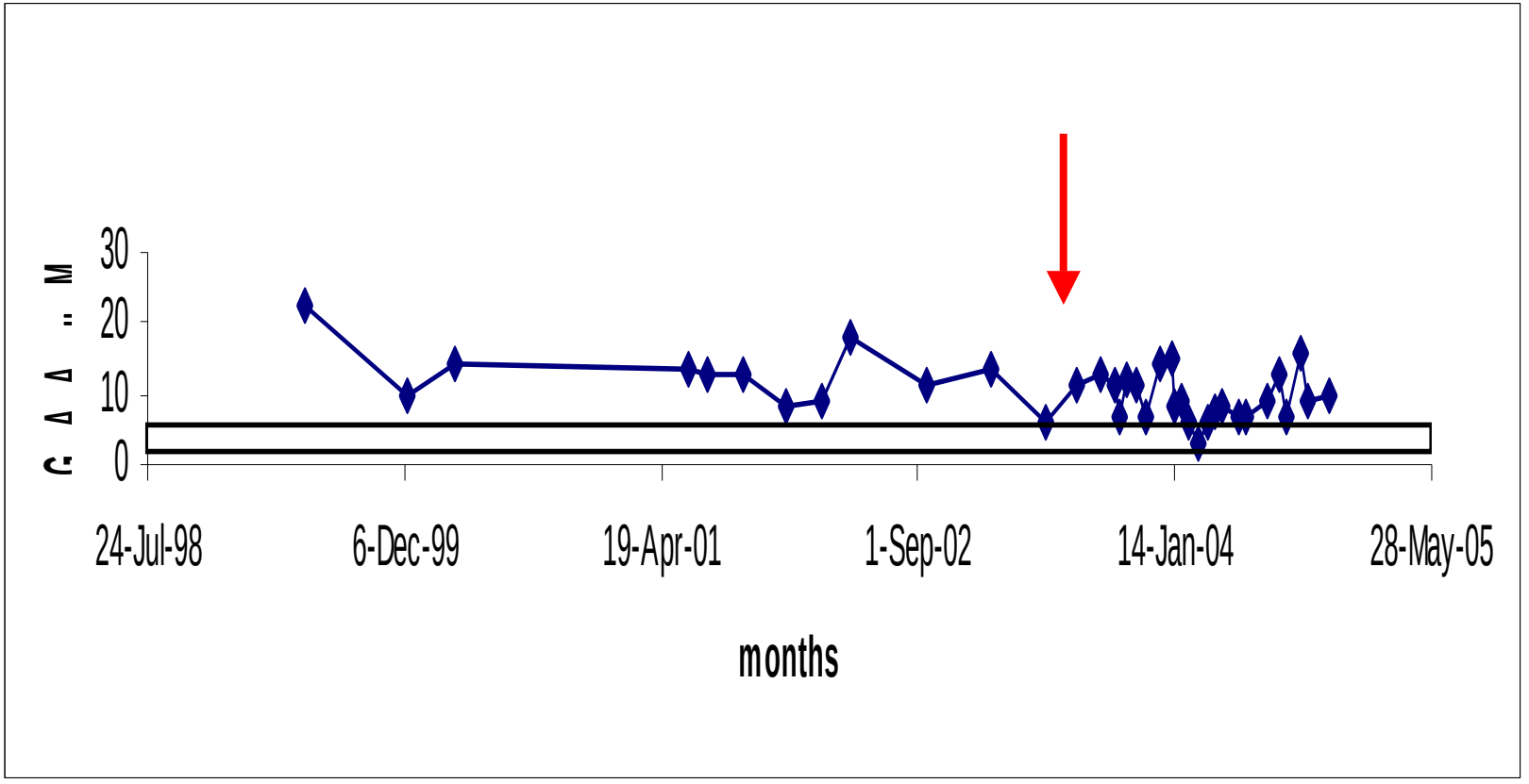
The treatment of GAMT deficiency

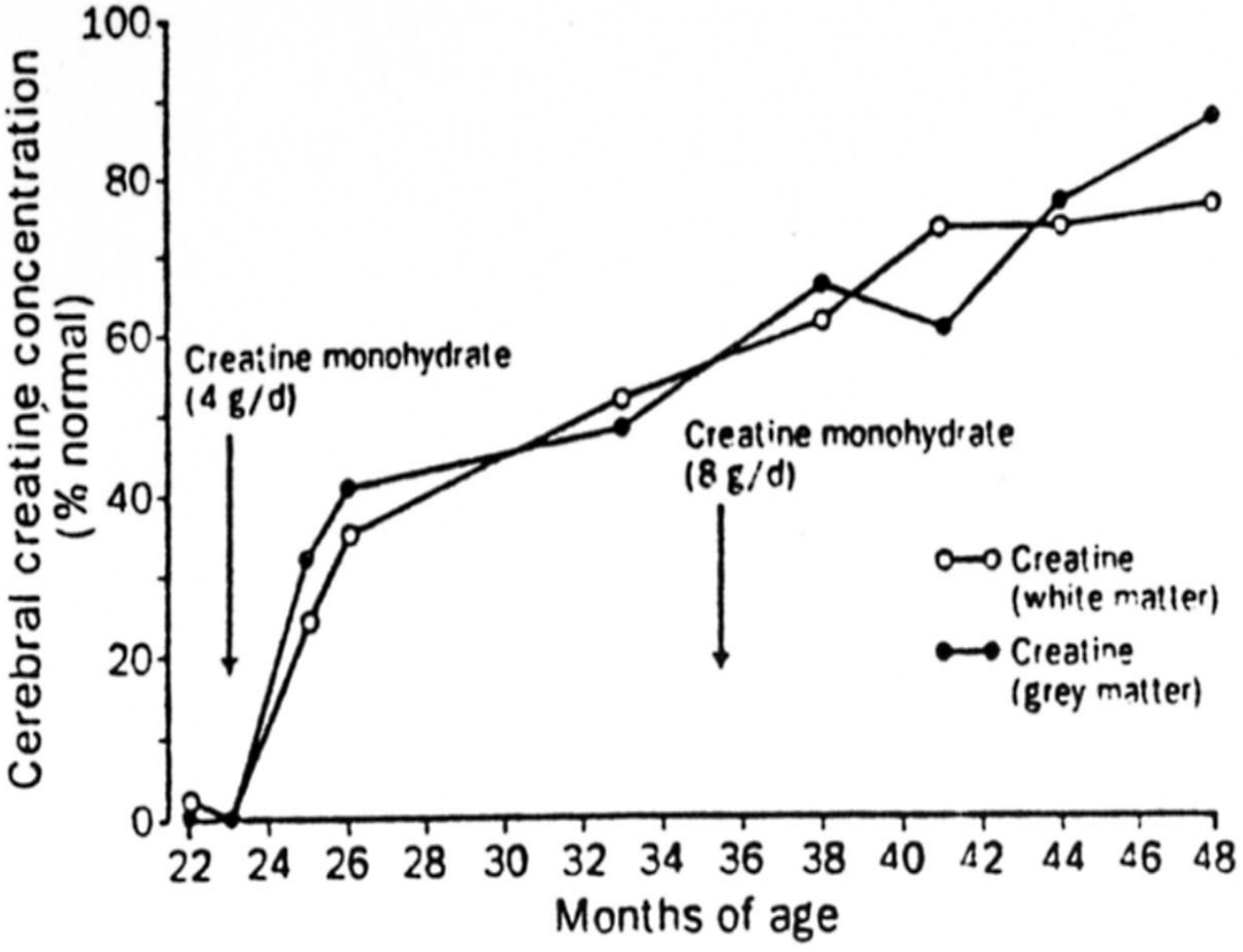
1) **Cr replenishment → Cr suppl (400-800 mg/kg bw/day)**
2) **↓ GAA synthesis:**
    1) **AGAT inhibition (Orn suppl 100 mg/kg bw/day)**

Cr homeostasis and treatment of GAMT deficiency

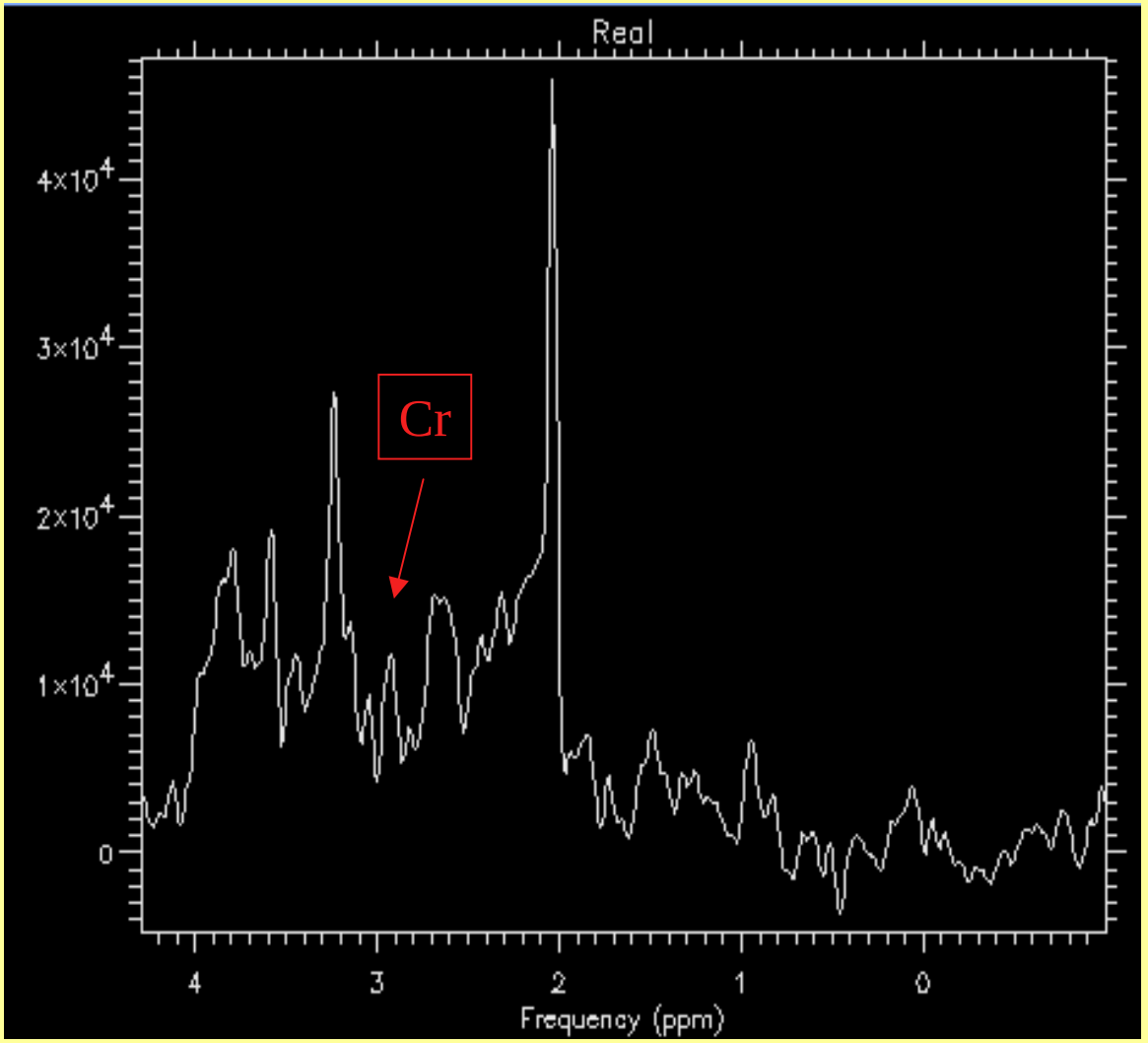


Case 1

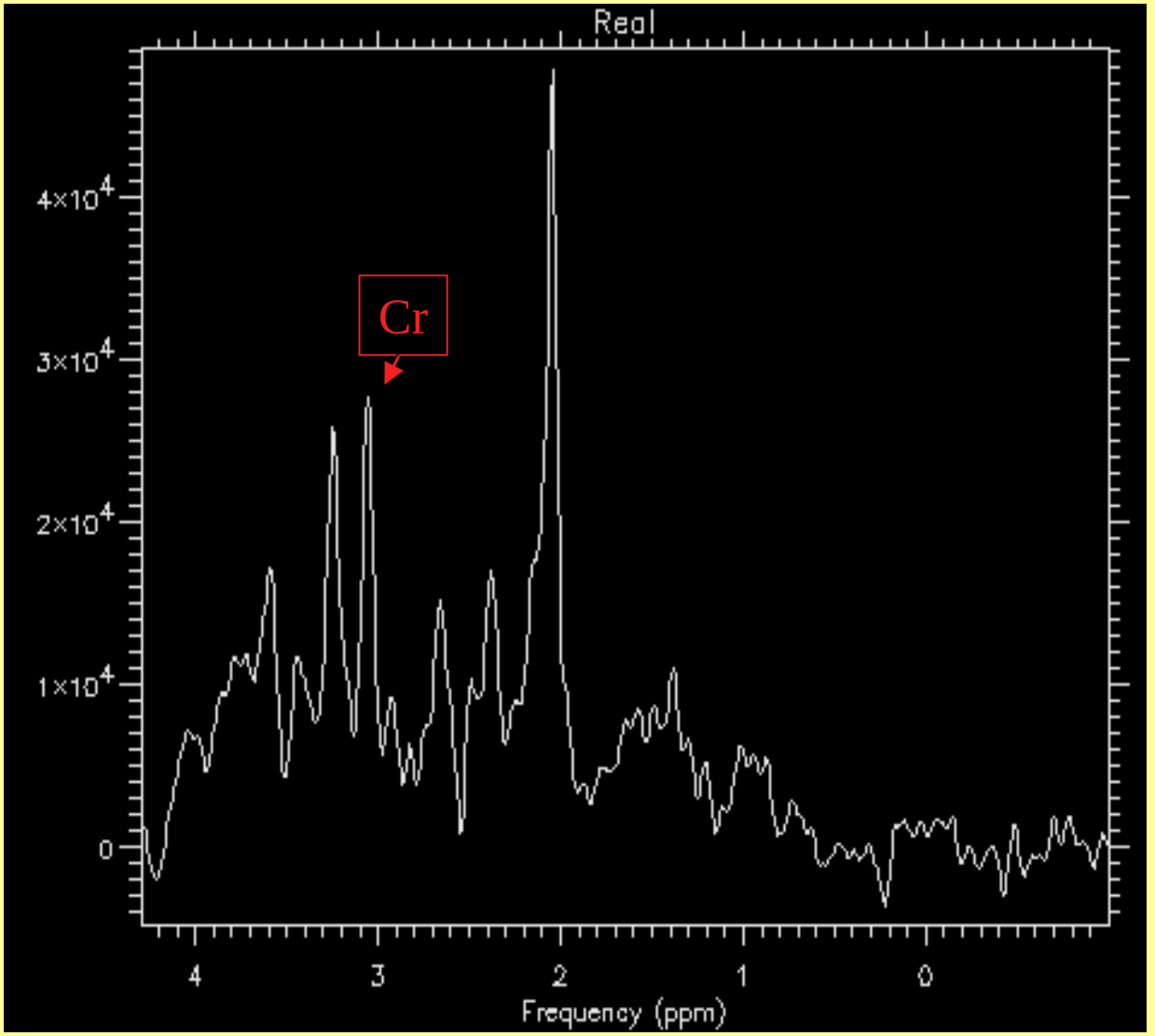

30
20
10
0
24-Jul-98
6-Dec-99
19-Apr-01
1-Sep-02
14-Jan-04
28-May-05
months



Stockler, Lancet 1996



Case 1 basal 1H-MRS examination



Case 1 1H-MRS after 16 months of therapy

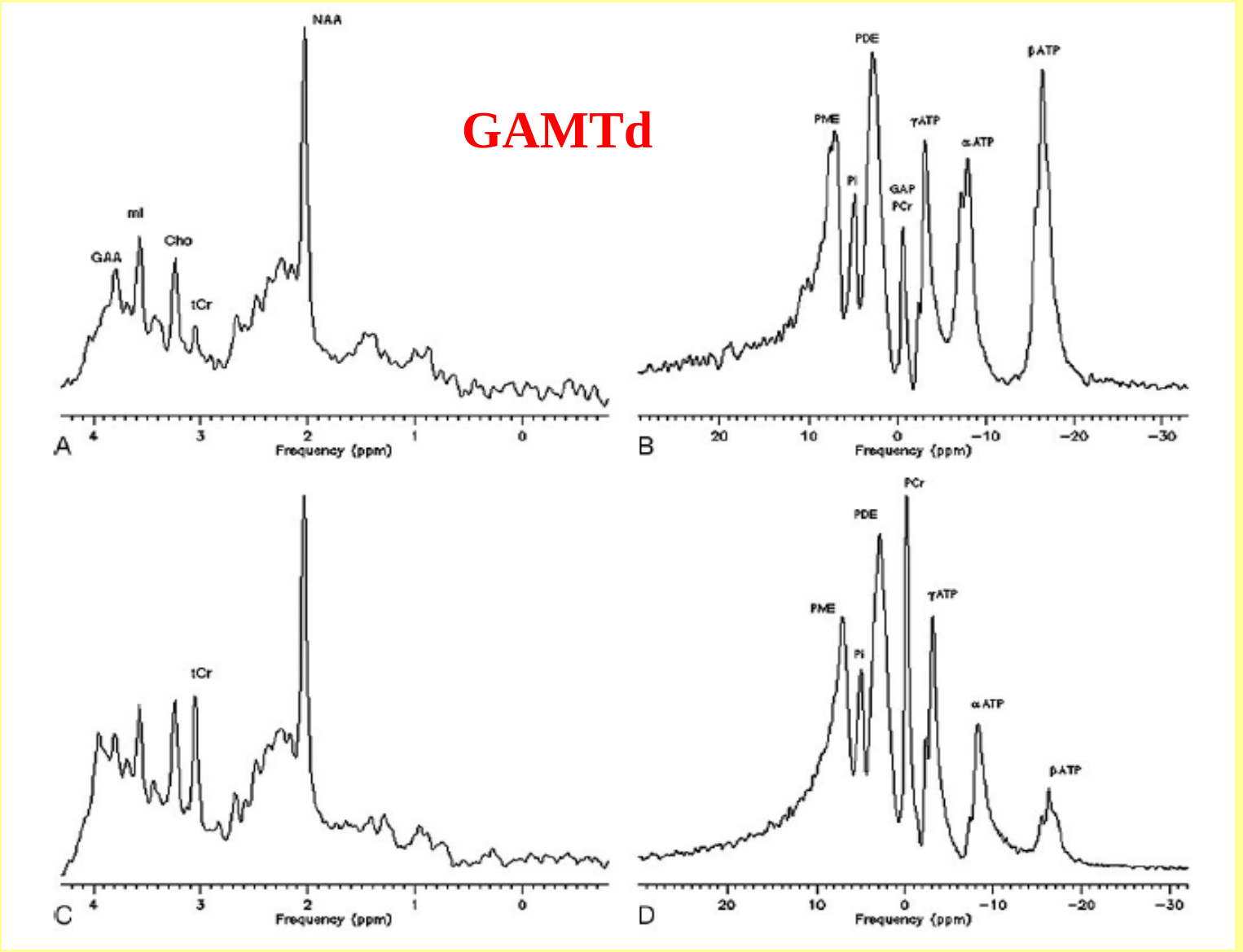
^{1}H-MRS

^{31}P-MRS

pretreatment

On treatment

GAMTd



Bianchi et al, 2007

Persistent increase of GAA: hypotheses

1. **GAA competes with Cr reabsorption at the sites of AGAT activity (kidney tubules) ⇒ ↓ suppression of AGAT**

2. **GAA downregulates Cr transporter at the level of GAA production ⇒ ↓ suppression of AGAT**

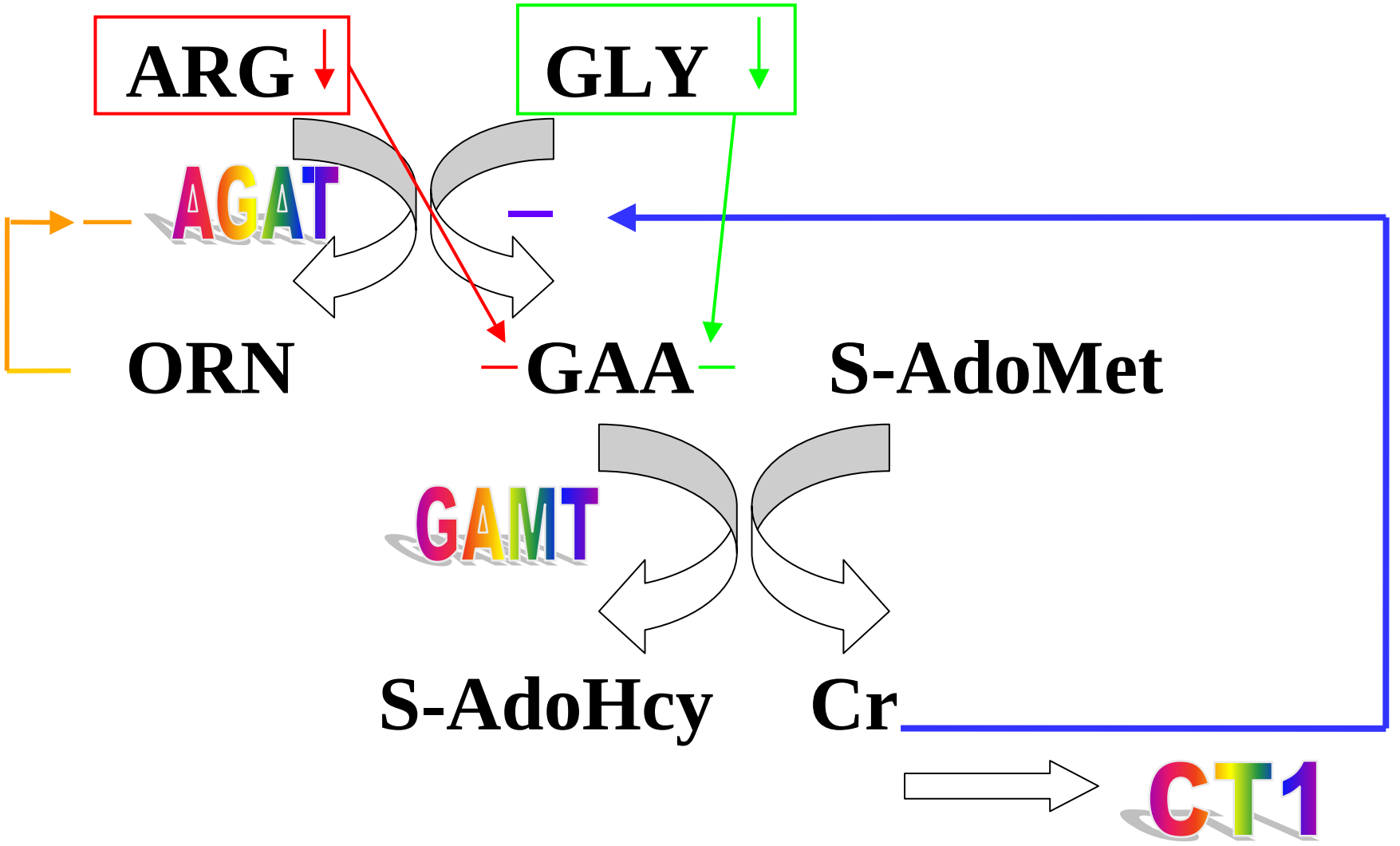
3. **A number of AGAT isoenzymes have been detected in the kidney: some are repressible by Cr, others not (Gross et al., 1988) ⇒ protracted deprivation of Cr could have favourite the expression of unrepressible AGAT isoforms**

The treatment of GAMT deficiency

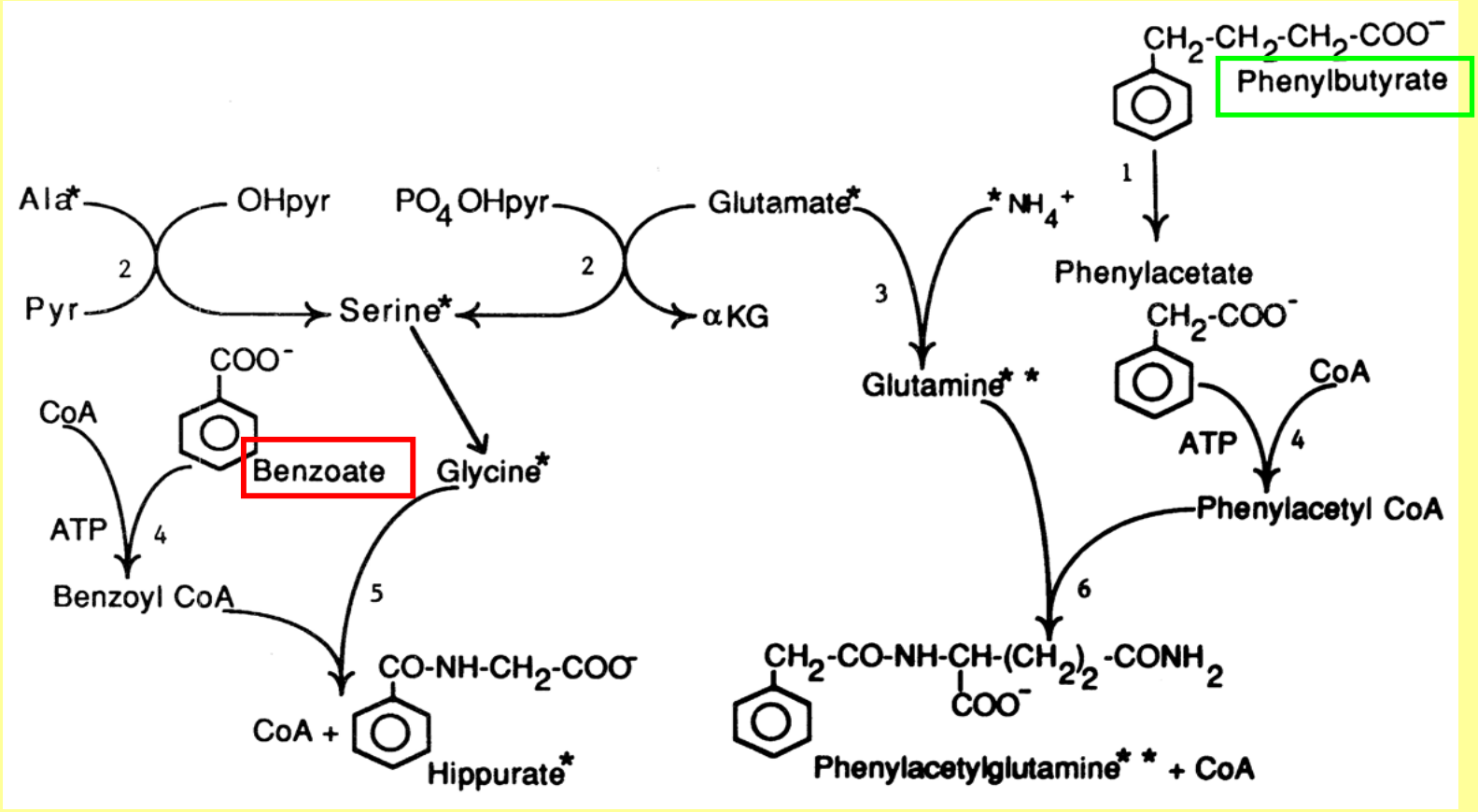
(Schulze, 2001; Ensenauer, 2004)

1) **Cr replenishment → Cr suppl (400-800 mg/kg bw/day)**
2) **↓ GAA synthesis:**
   - **AGAT inhibition (Orn suppl 100 mg/kg bw/day)**
   - **substrate restriction (↓ Arg 15/mg/kg bw/day; proteins 1g/kg bw/day)**
   - **substrate restriction (↓ Arg: sodium phenylbutyrate, 100 mg/kg bw/day; ↓ Gly: sodium benzoate, 100 mg/kg bw/day)**

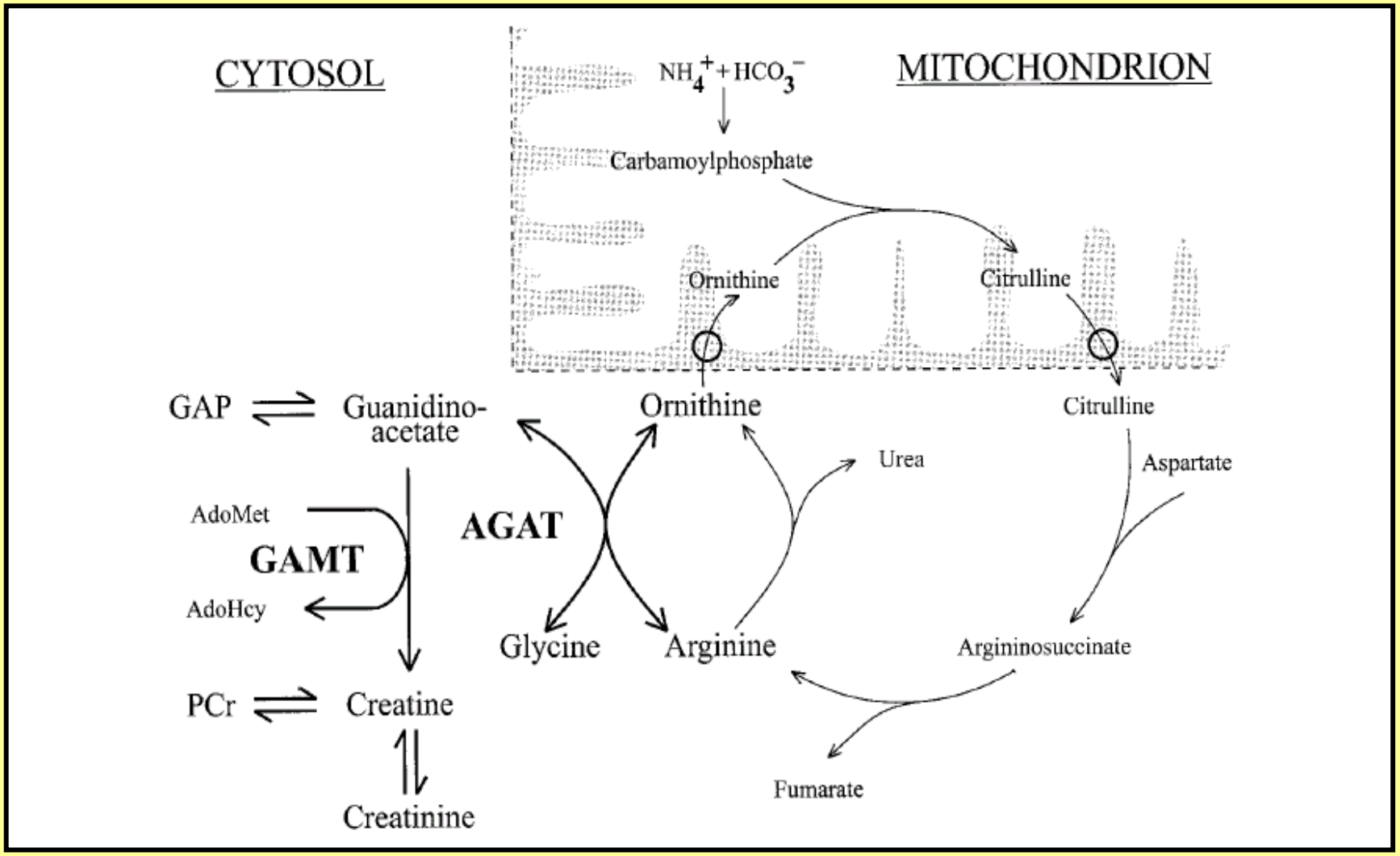
Cr homeostasis and treatment of GAMT deficiency



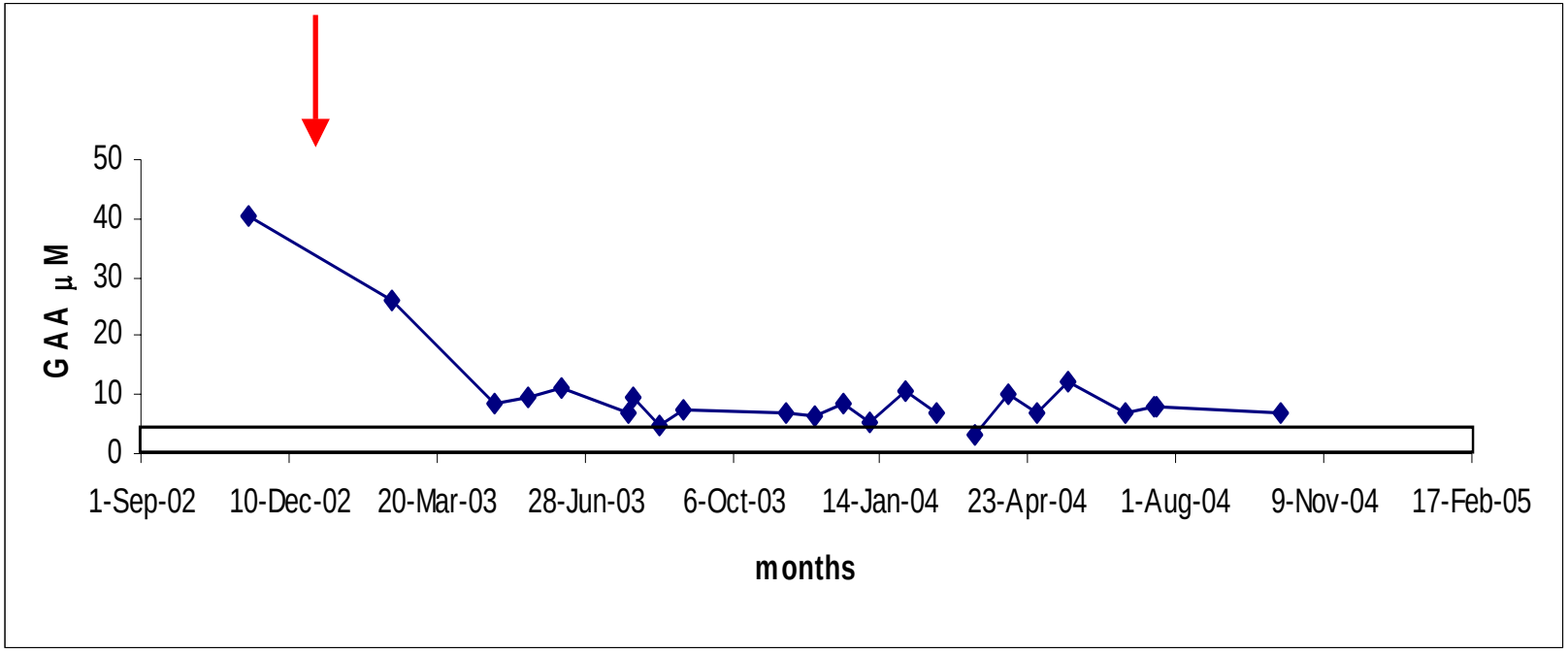
Substrate restriction: Sodium phenylbutyrate and benzoate



Cr metabolism



Case 2


50
40
30
20
10
0
GAA µM
1-Sep-02
10-Dec-02
20-Mar-03
28-Jun-03
6-Oct-03
14-Jan-04
23-Apr-04
1-Aug-04
9-Nov-04
17-Feb-05
months

AGAT enzyme inhibition by high-dose ornithine

Ornithine (aspartate): 350-800 mg/kg bw/day

- **↓ 45% GAA (plasma)**
- **↓ 60% GAA (urine)**
- **↓ ↓ GAA synthesis**

Dietary Arg restriction + high-dose Orn

↓↓↓ GAA

No metabolic acidosis or diarrhea (as with Orn hydrochloride)

Schulze et al. 2005

The prognosis of late detected (and treated) GAMT deficiency

Improvement (+):

- Seizures (+++)
- Dystonic-dyskinetic mov dis (+++)
- Pallidal alterations (+++)
- Mental retardation mild (1/27) to severe (+)
- Severe language retardation (26/27): (+)
- Behavioral disorders ?

Mercimek-Mahmutoglu et al, 2007

Successful treatment of a guanidinoacetate methyltransferase deficient patient: Findings with relevance to treatment strategy and pathophysiology

Krijn T. Verbruggen [a,*], Paul E. Sijens [b], Andreas Schulze [c], Roelineke J. Lunsing [d], Cornelis Jakobs [e], Gajja S. Salomons [e], Francjan J. van Spronsen [a]

Biochemical and developmental results of treatment of a guanidinoacetate methyltransferase (GAMT) deficient patient with a mild clinical presentation and remarkable developmental improvement after treatment are presented. Treatment with creatine (Cr) supplementation resulted in partial normalization of cerebral (measured with magnetic resonance proton spectroscopy) and plasma levels of Cr and guanidinoacetate (GAA). Addition of high dose ornithine to the treatment led to further normalization of plasma GAA, while cerebral Cr and GAA did not improve further.

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Molecular Genetics and Metabolism 91 (2007) 294–296

First presymptomatic treatment in a newborn with GAMT deficiency

Brother of an affected patient

- **↑ GAA in cord blood**
- **↑↑ blood GAA during the first 24 hrs of life**

Blood Cr normal (→no diagnostic value of Cr in newborns)

Treatment onset: 5 days of life

Treatment:

- **Cr (400 mg/kg bw/day)**
- **Orn aspartate (800 mg/kg bw/day)**
- **Sodium benzoate (100 mg/kg bw/day)**

Outcome (24 months): normal psychomotor development, no side effects

Schulze et al, 2006

The treatment of AGAT deficiency

Cr monohydrate supplementation

- young and adult subjects 200- 400 mg/kg bw/day
- < 1 year 100 mg/kg bw/day

Bianchi et al. 2000, Bianchi & Battini, unpublished data

Cr synthesis

Urea cycle

gly

arg

AGAT

orn

gaa

S-adomet

Kidney

GAMT

S-adohcy

Liver

Cr

CT1

Muscle, Brain

ATP

ADP

Cr

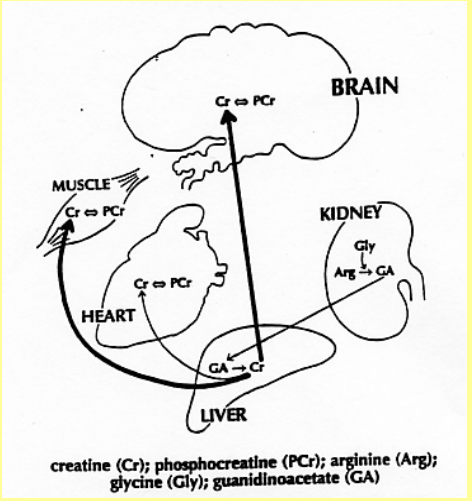
CK

PCr

Cr

Crn

Urinary escretion



creatine (Cr); phosphocreatine (PCr); arginine (Arg); glycine (Gly); guanidinoacetate (GA)

The outcome of AGAT deficiency

Case 1 (age 11)

- **Pre-treatment (age 4.3 yrs)**
- Absence of language
- GDS performance score 42
- GDS eye-hand coordination 57
- VMI invaluable
- **After 16 mo of treatment**
- GDS performance score 68
- GDS eye-hand coordination 57
- VMI 77
- **Present status**
- Mild mental retardation

Case 2 (age 13)

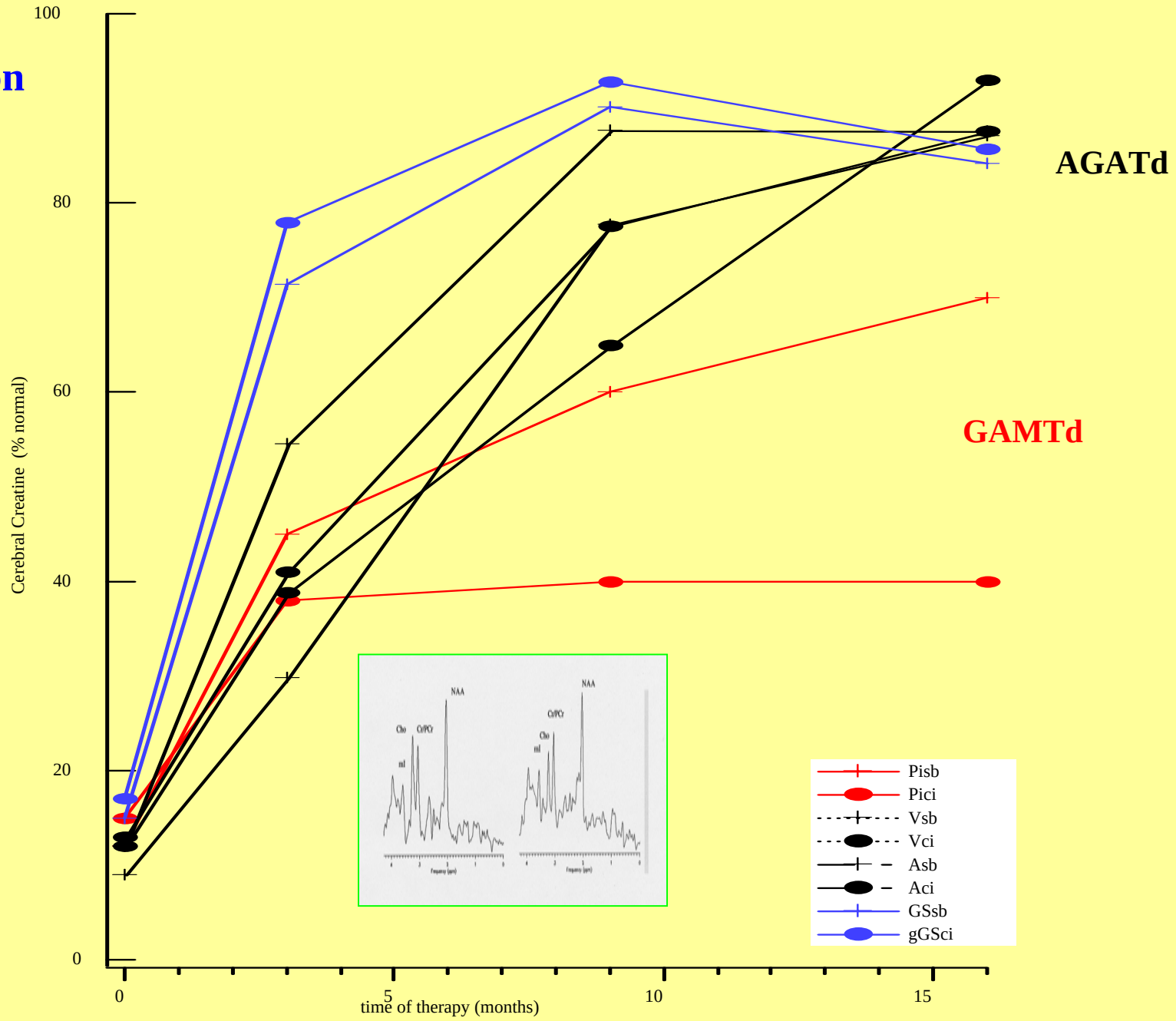
- **Pre-treatment (age 6.5 yrs)**
- Absence of language
- LIPS IQ 65
- VMI 60
- **After 16 mo of treatment**
- LIPS IQ 65
- VMI 77
- **Present Status**
- moderate mental retardation

ARGININE:GLYCINE AMIDINOTRANSFERASE (AGAT) DEFICIENCY IN A NEWBORN: EARLY TREATMENT CAN PREVENT PHENOTYPIC EXPRESSION OF THE DISEASE

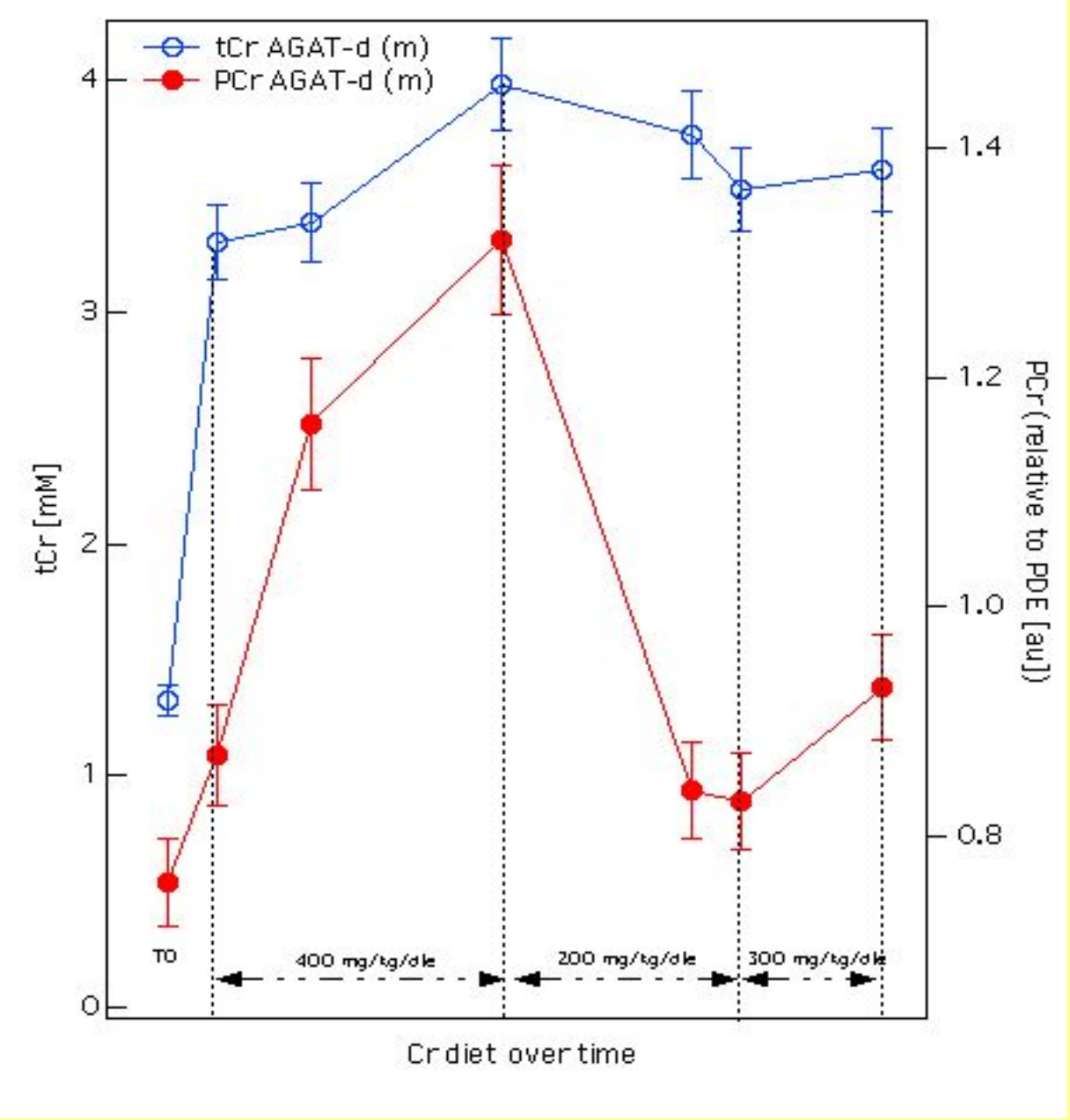
ROBERTA BATTINI, MD, PHD, M. GRAZIA ALESSANDRÌ, PHD, VINCENZO LEUZZI, MD, FRANCESCA MORO, PHD, MICHELA TOSETTI, PHD, MARIA C. BIANCHI, MD, AND GIOVANNI CIONI, MD

Arginine:glycine amidinotransferase deficiency is a treatable inborn error of creatine synthesis, characterized by mental retardation, language impairment, and behavioral disorders. We describe a patient in whom arginine:glycine amidinotransferase was diagnosed at birth and treated at 4 months with creatine supplementation. In contrast with his 2 older sisters, he had normal psychomotor development at 18 months. *(J Pediatr 2006;148:828-30)*

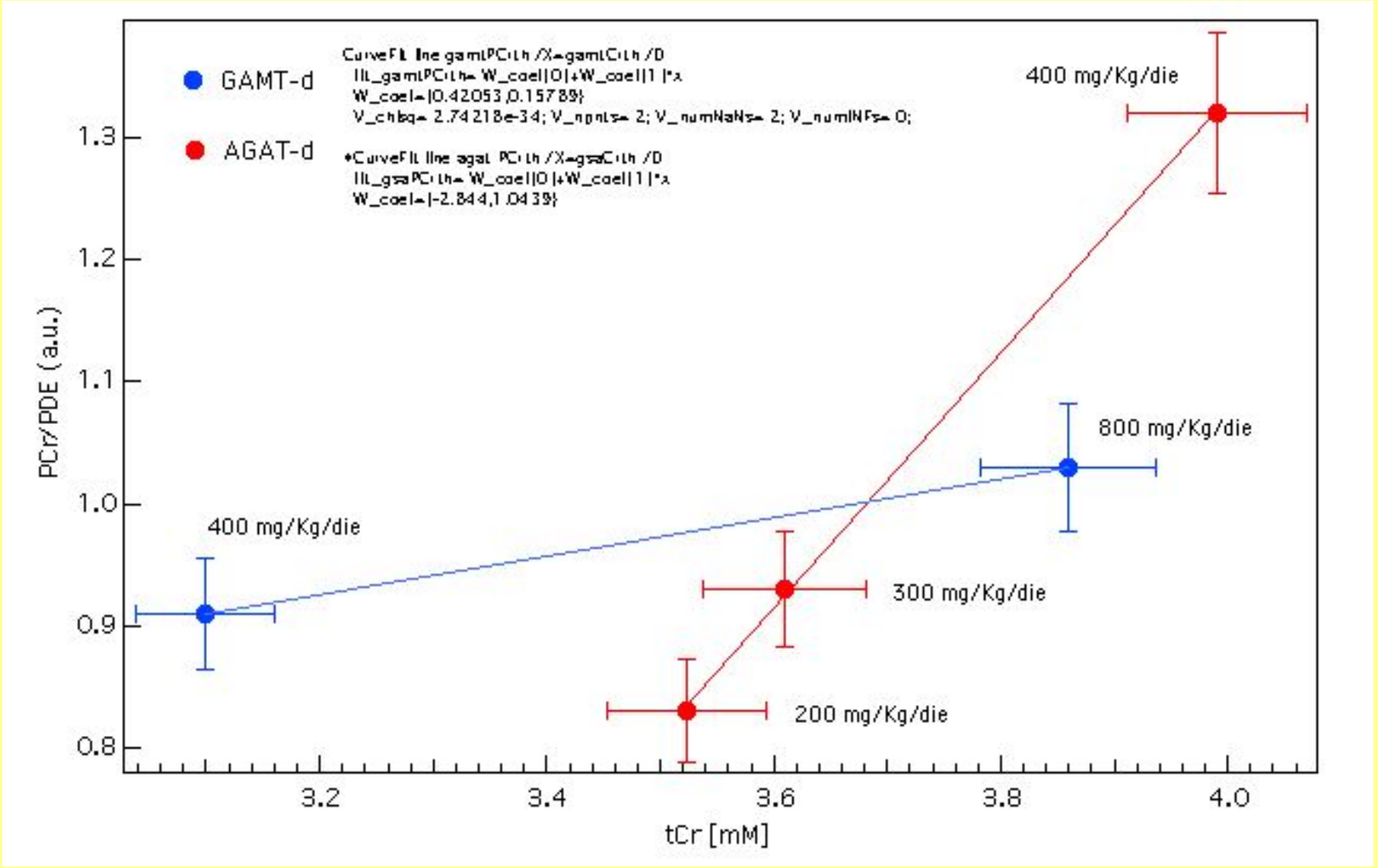
Brain Cr on ^{1}H-MRS



Bianchi et al, unpublished



Bianchi et al, 2007



Bianchi et al, 2007)

Comments

- **GAMT and AGAT deficiencies are rare conditions**
- **An early treatment improves significantly the outcome of these disorders (GAMT>AGAT)**
- **A neonatal presymptomatic diagnosis of GAMT and AGAT is possible and inexpensive**
- **GAMT and AGAT deficiencies are candidate conditions for neonatal screening programs**

Puzzling aspects in GAMT, AGAT and CT1 deficiencies

- **The lack of skeletal and cardiac muscle involvement**
- **The selective impairment of mental and language functions**

The selective impairment of mental and language functions

(Watanabe et al., 2002)

- **Cr supplementation reduces mental fatigue in subjects repeatedly performing simple matematical calculations**
- **Cr supplementation increases oxygen utilization in the brain (near infrared spectroscopy)**
- **Hypothesis: increased capacity of OXPHOS by Cr leads to decreased lactate → less mental fatigue**

The selective impairment of mental and language functions: unknown aspects

- **Cr and CNS development**
- **Cr and mental functioning during postnatal brain development**
- **Cr and early language development**
- **Cr and learning**

Cr disorders: differential diagnosis

Clinical features	AGAT	GAMT	CT1
REDUCED SOMATIC GROWTH	●		●
EARLY ONSET	●	●	●
NEUROLOGICAL DETERIORATION		●●●	●
EPILEPSY		●●●	●
MOVEMENT DISORDERS		●●	●
HYPOTONIA	●	●	●
MENTAL RETARDATION	●	●●●	●●
LANGUAGE DERANGEMENT	●●●	●●●	●●●
AUTISTIC SPECTRUM	●	●	

The epidemiology of MR: prevalence

- **Severe MR → 3-4/1000**
- **Mild MR → 5.4-10.6/1000**
- **Age-specific rate: ↑ 0→10-14 yrs; > 14 yrs ↓**
- **M/F ratio → 1.6-1.7 (up to 15 yrs)**

The etiology of mental retardation

(P Strømme & G Hagberg, 2000)

- Population based study: 30037 children
- 178/30037 (0.59%) subjects with MR
- 79 severe/99 mild
- **63/178 (35.3%) → Genetic disorders**
  - 15/63 → Single gene disorders
  - 21/63 → chromosomal disorders
  - 6/63 → neurodegenerative/neurodevelopmental
  - 14/63 → familial MR
- 34/178 (19.1%) → Unknown
  - 20/34→ dysmorphic/unspecified syndromes
  - 14/34→ brain anomaly

Diagnostic investigations in individuals with unexplained MR (metanalysis)

(van Karnebeek et al, 2005)

- **Cytogenetic study** → 9.5%
  severe MR > mild MR (13.3% vs 4.1%)
- **Subtelomeric studies** (FISH) → 4.4%;
- **Fragile X** → 5.4% (cytogenetic studies);
  → 2 % (molecular studies);
- **Dysmorphology** → 38-91%
- **Metabolic investigations** → 1%
- Neurological examination → 42.9%
- Neuroimaging studies → 30%

Linee guida RM: ed indagini metaboliche

Anche in assenza di segni clinici suggestivi,

<u>i seguenti esami metabolici dovrebbero essere effettuati</u>

<u>in tutti i casi di RM</u> in assenza di diagnosi alternative:

- ***aminoacidi plasmatici***
- ***acidi organici urinari***
- ***dosaggio acilcarnitine***
- ***dosaggio ematico di Cr e Gaa***
- ***rapporto Cr/Crn nelle urine (bambini con evidenza di RM X-linked)***

Deficit di Cr e malattie rare: peculiarità ed opportunità

- **Nuova famiglia di disturbi del metabolismo energetico**
- **Diagnosi: bassa specificità clinica/alta complessità diagnostica**
- **Disponibilità di un trattamento efficace in 2 deficit (GAMT, AGAT), anche efficace nel prevenire l'espressione fenotipica della malattia (trattamento pre-sintomatico)**
- **Opportunità: studio del rapporto fra metabolismo energetico, funzioni cerebrali e loro sviluppo**
- **Opportunità: possibile approccio terapeutico ad altre malattie neurodegenerative**

Deficit di Cr e malattie rare: problematiche aperte

- **Incidenza della patologia: rarità vs difficoltà diagnostiche**
- **Ancora scarsa visibilità della rete nazionale**
- **Fisiopatologia: ruolo e funzioni della Cr nel SNC maturo ed immaturo**
- **Mancanza di un modello patogenetico soddisfacente**
- **Un solo modello animale disponibile (deficit di GAMT)**
- **Non terapia per il deficit di CT1**
- **Efficacia della Cr e/o dei suoi precursori nelle malattie neurodegenerative ?**
- **Cr e prevenzione del danno ipossico ?**

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