Creatine Deficiency Syndromes
Clinical Presentation

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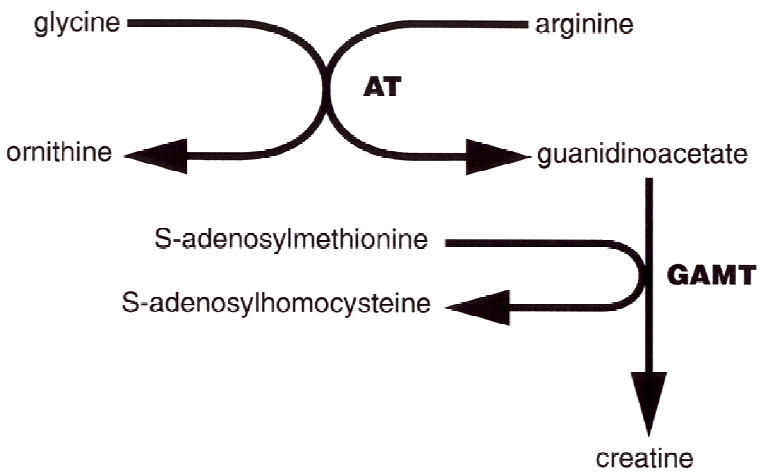
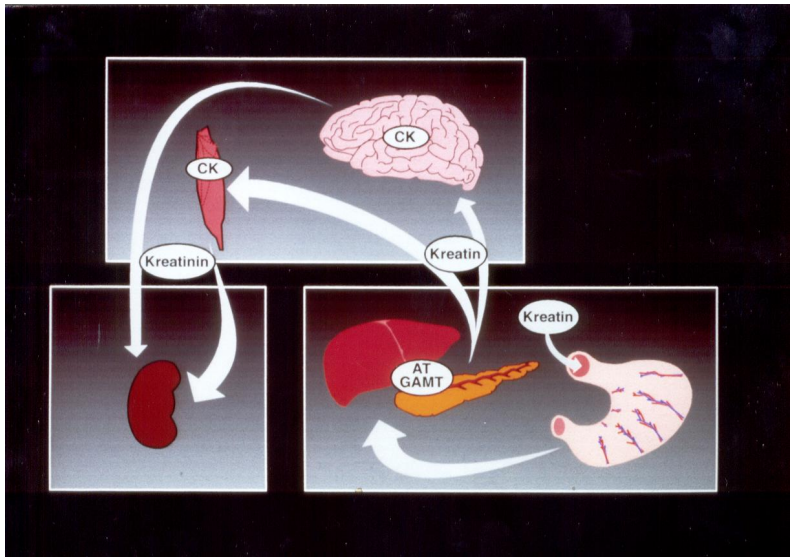
Creatine Synthesis, Creatine Metabolism & Inborn Errors of Creatine Metabolism





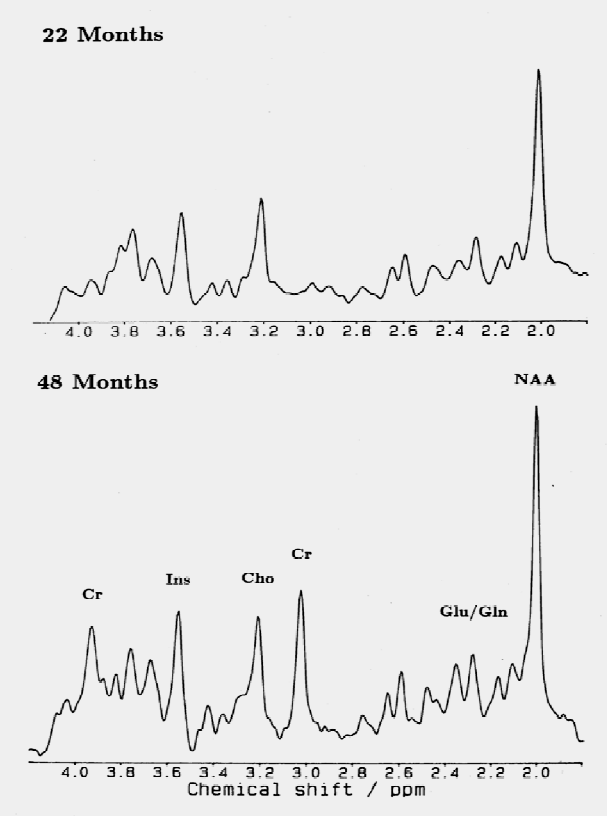
„Creatine Deficiency Syndromes“

1994 GAMT Deficiency (Stöckler et al)

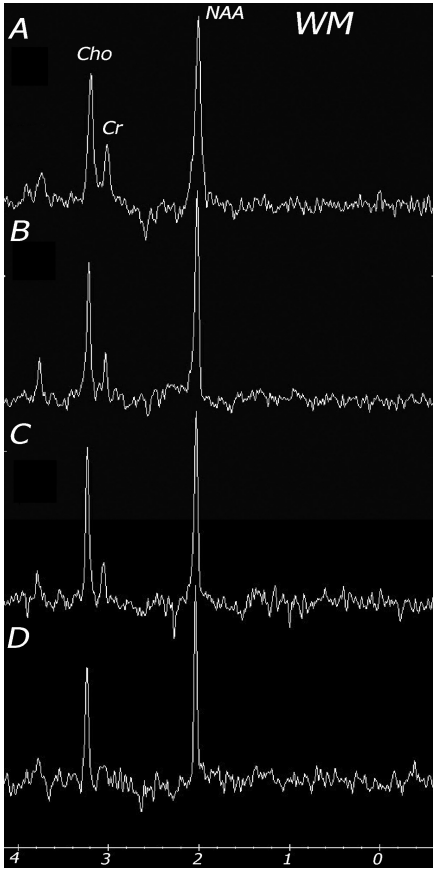
2001 AGAT Deficiency (Item et al)

2001 Creatine Transporter Deficiency (Salomons et al)

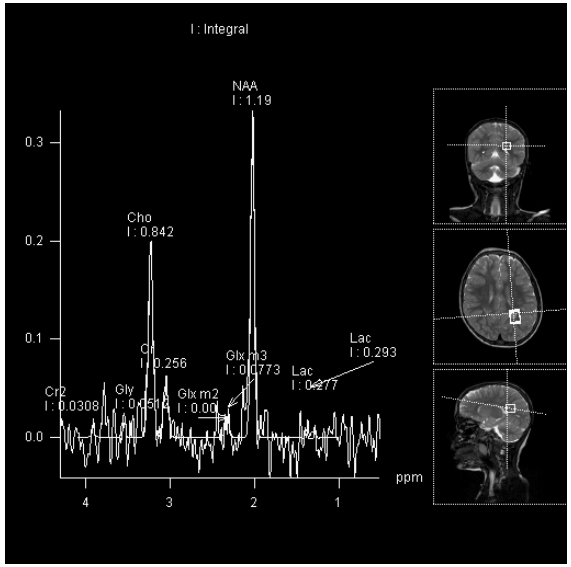
Creatine Deficiency Syndromes: Common Biochemical Endpoint



GAMT



AGAT



CRTR female

CDS: Clinical Features

	MR	Epilepsy	EPMD	Urinary metabolites
GAMT	+(++)	+(++)	(+++)	GAA high
AGAT	+(+)	+	(+)	GAA low
CRTR	+(++)	+(+)	(+)	Cr/Crt high

CDS: Numbers of Patients by 2008

GAMT	N=50-60 1 neonatal diagnosis (Schulze) $\geq$ 1 PD (GAA, mutation) (Cheillan 2006)
AGAT	N= 7 from 3 families (F1=4; F2=1; F3=2) 1 neonatal diagnosis (Battini 2006) 1 PD (Johnston 2005)
CRTR	>> 150 1-3% male / X-linked MR

GAMT Deficiency: Features in 27 Patients

(Mercimek-Mahmutoglu et al, Neurology 2006; 67: 480-4)

- Europe, Turkey, Middle East
  - Portugal n=10
  - Turkey n=7
- Onset of first symptoms: 3 - 6 mo / 3 y
- Age at diagnosis: 2 y (2-29)

Type & degree of clinical manifestation in 27 GAMT patients

Type manifestaion & Degree severity	MR 27/27	Epilepsy 25/27	EPMS 15/27	Σ Phenotype
severe	21	7	6	12
moderate	3	13	7	12
mild	3	5	2	3

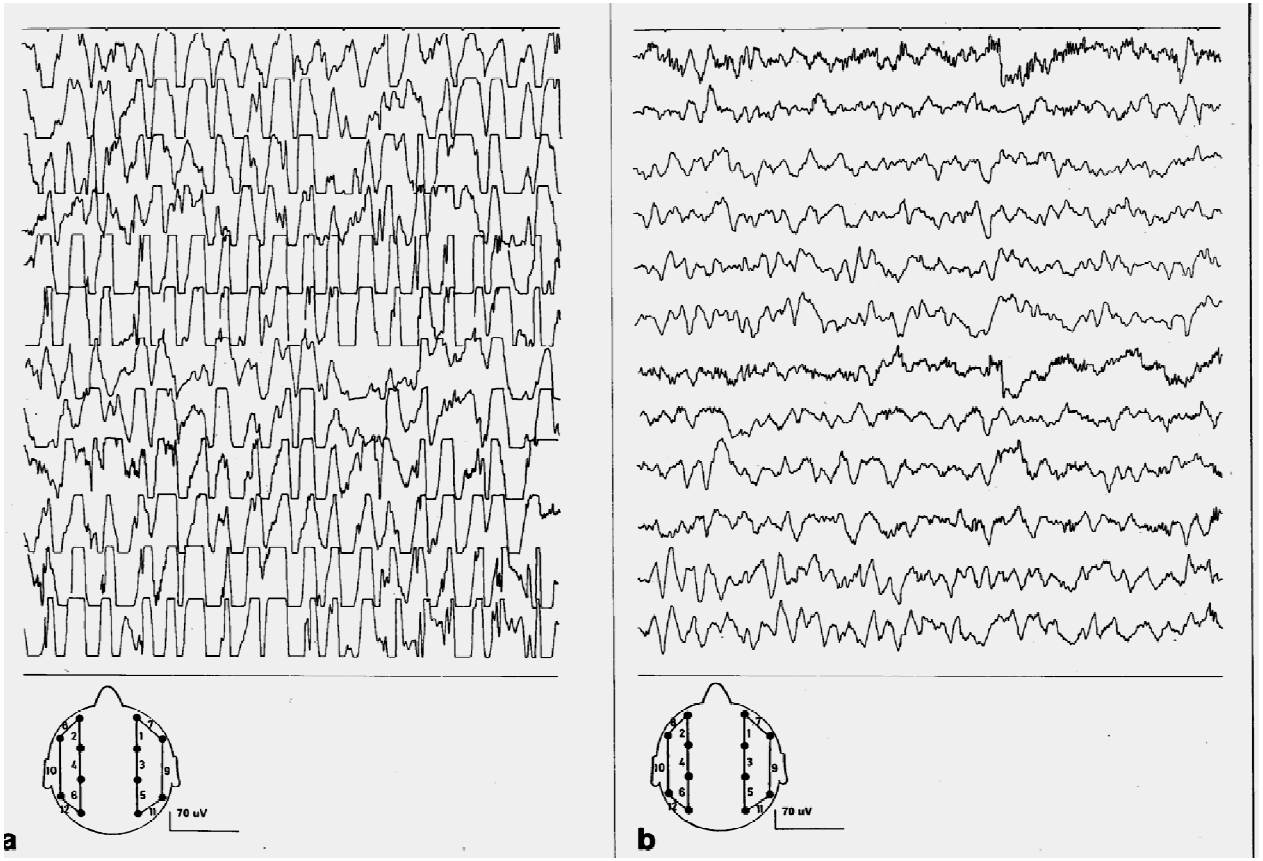
Mahmutoglu et al Neurology 2006

GAMT-D: Seizures & EEG

- Seizures (25 / 27)
  - Myoclonic
  - Gen tonic clonic
  - Partial complex
  - Head nodding
  - Drop attacks

- EEG (15 / 27)
  - High amplititude theta-delta background , multifocal spikes (9/15)
  - Hypsarrhythmia (1/15)
  - Focal sharp waves (4/15)
  - Normal despite febrile seizures (1/17)

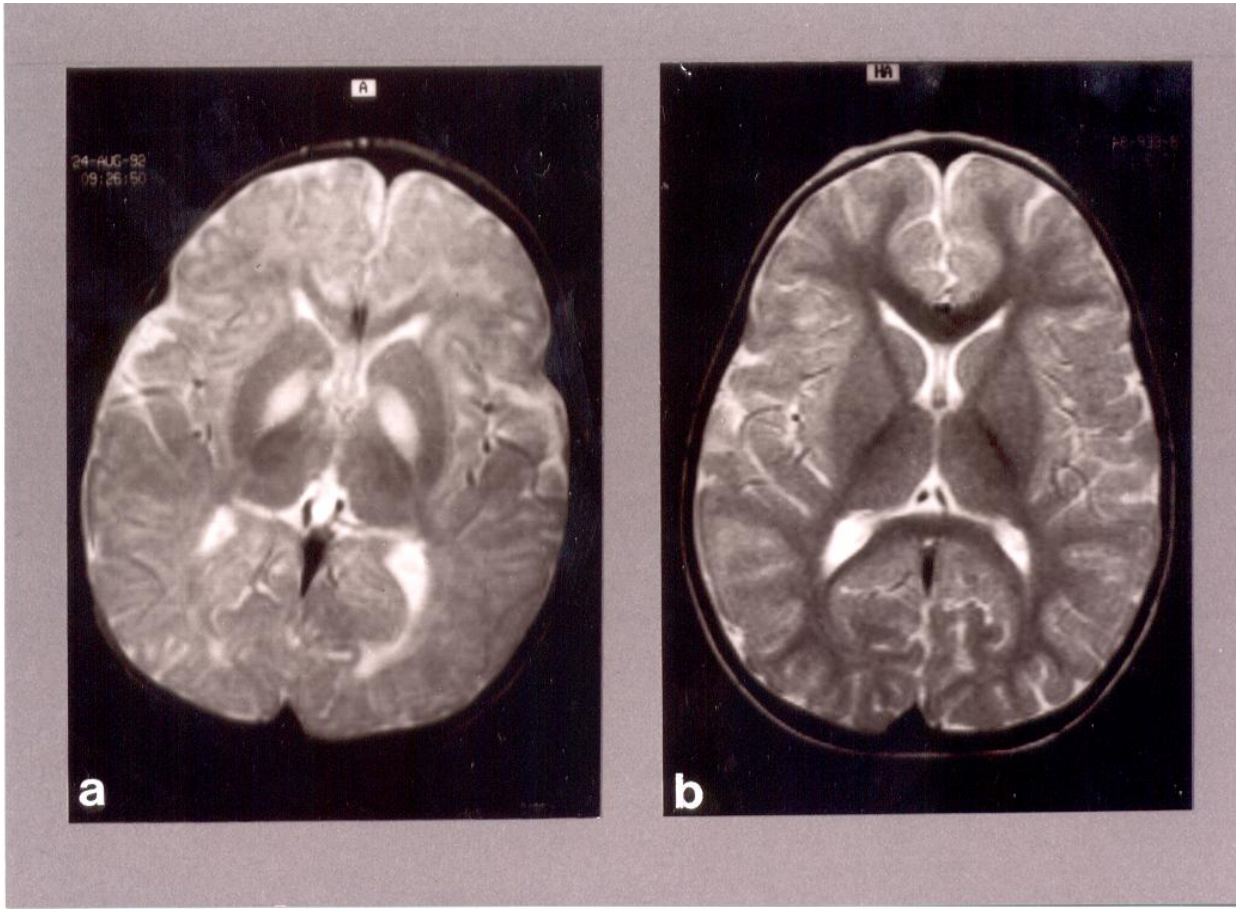
High amplititude theta-delta background, multifocal spike EEG in GAMT-D



GAMT-D: Movement disorder & Brain MRI

- Movement disorder (15/27, 48%)
  - Chorea
  - Hemiballism
  - Athetosis
  - Dystonia / spasticity
  - Ataxia
  - (choreatic storm)
- Brain MRI (22/27)
  - Bilateral signal intensities in globus pallidus (6/22)
  - Associated with movement disorder (4/6)

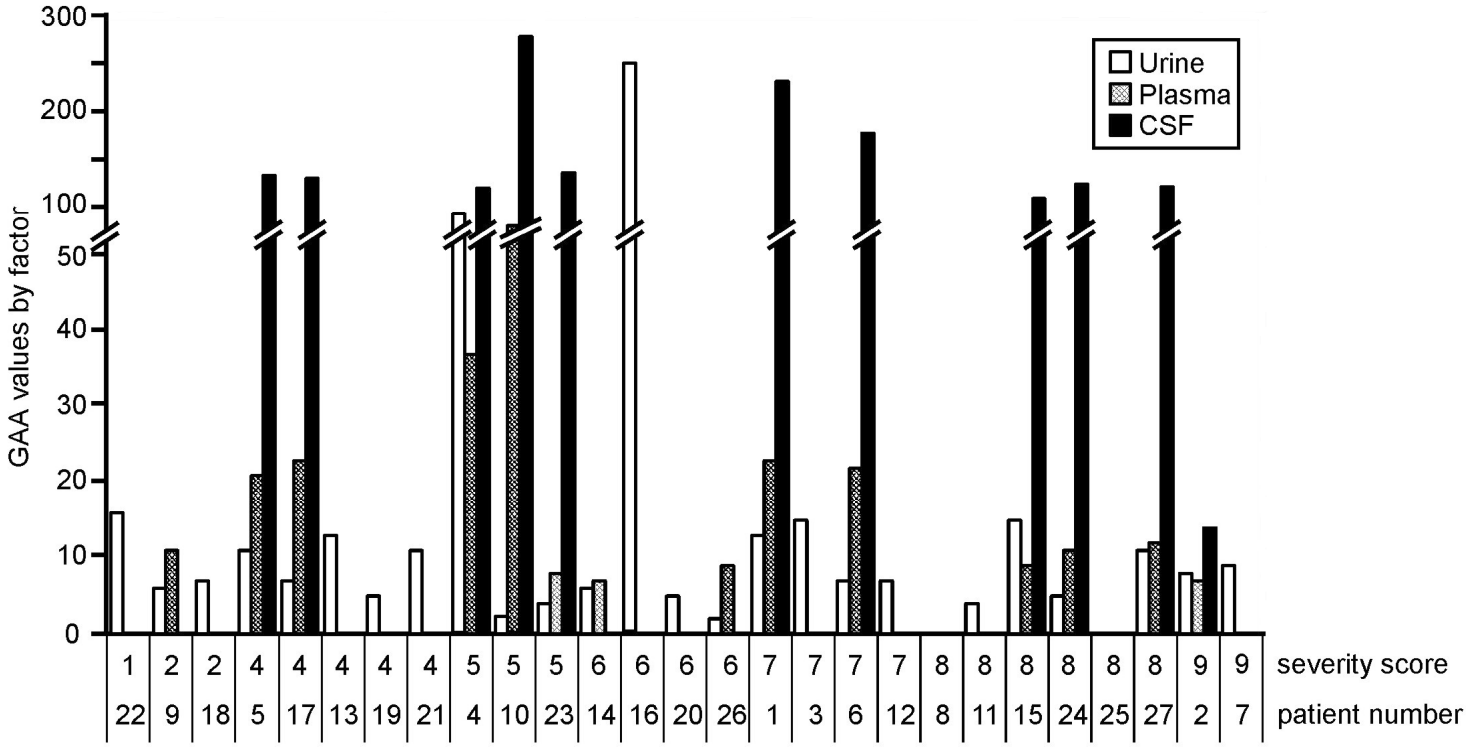
Bilateral signal intensities in globus pallidus in GAMT-D



GAMT-D: Behaviour & Speech

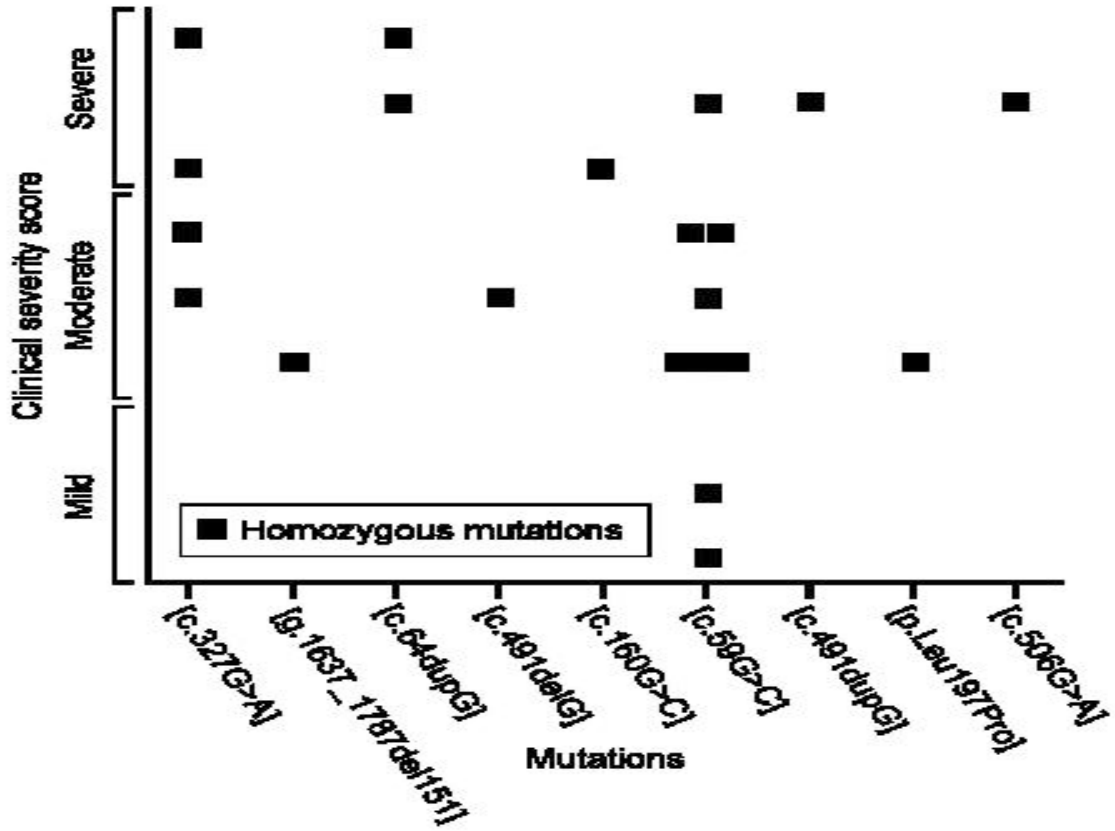
- Behavioural abnormalities (21/27)
  - Hyperactivity
  - Autistic
  - Self injurious
- Speech delay (21/27)
  - Less than 10 words irrespective of degree of MR and age

Clinical severity & degree GAA accumulation



Mahmutoglu et al Neurology 2006

Clinical severity & genotype



Mahmutoglu et al Neurology 2006

Response to treatment* in 23/27 patients

*23 / 27 Creatine-monohydrate;
5 / 23 plus arginine restricted diet and ornithine suppl

	MR	**Epilepsy**	**Movement Dis**	**GAA**
Improve-ment	0 / 23 0 %	19 / 23 86 %	7 / 12 58%	U: 0-80% P: 0-90% CSF: 50-85%

Mahmutoglu et al Neurology 2006

GAMT 1st neonatal diagnosis

Schulze et al Neurology 2006

GAA blood spot	>99.5%
GAA urine	Elevated from birth, increase during 3 weeks
Creatine brain	Low at birth
Treatment creatine&dietary arginine restriction	Normal development at 14 mo

AGAT Deficiency

Clinical manifestations in 7 patients

	Family1 n=4	Family2 n=1	Family3 n=2*
Dev delay	+	+	+
Speech delay	+	+	+
MR-ID	+	(+)	+
Occasional seizures	+	+	-
Dystrophy	+	?	+
Age	0-≤10	<5y	14, 20 y

*Elpeleg personal commun, aug 2008

AGAT Mutations in 5 (7) Patients

T149X/T149X

(Stop codon)
(8/8)

IVS3+1G>T
(donor splice site)
Skipping exon 3
(2/2)

P1, P2: Item, Am J Hum Genet 2001
P3: Battini, Mol Genet Metab 2002
P4: Battini, J Pediatr 2006

P5: K Johnston, pers comm 2005

(P6,7): Elpeleg pers comm 2008

AGAT-D: Effect of early creatine supplementation on development

Italian Family

Treatment: 100-400 mg/kg creatine monohydrate

13 yr-old & 11yr-old siblings (P1, P2):

creatine supplementation initiated at ages 7 and 5 yr, still moderate mental retardation

8 yr-old cousin (P3):

creatine supplementation initiated at age 2 yr, borderline IQ

4 mo-old (P4):

PD, creatine supplementation started early at age 4 mo. normal development at 18 mo *(Battini 2006)*

AGAT-D: Biochemical effect of Creatine in 1st neonatal diagnosis (Battini J Pediatr 2006)

age	DQ	Cr (b)	Cr (p)	Cr (u)	Ga (u)
normal	100	100%	18-140	200-5500	55-700
0-4		low	3-16	6-24	0.3-0.5
5		-	222	1750	nd
8		-	164	4320	nd
11		-	172	5350	nd
17	105	60%	67	1270	nd
29		60%			

Salomons et al, 2001; Cecil et al, 2001

X-linked creatine transporter (CRTR) (SLC6A8) deficiency

- Male offsprings: mental retardation & absent speech development
- Females: learning handicaps
- Seizures, responsive to conventional medication
- Cerebral creatine deficiency; no increase of cerebral creatine upon substitution!

CRTR Deficiency: Frequency

- > 150 patients identified
- Symptomatic female carriers
- 2% X-MR (Rosenberg 2004)
- 1% male MR (Clark et al 2006)
- 2 definite diagnoses in 157 males (1-18y) („metabolic screening“) (2.3%) (Mahmutoglu)
- Prevalence in autism? 100 males autism spectrum disorder, 1 unclassified variant (Newmeyer, Neuropediatrics 2007)

CRTR Deficiency: X-MR plus

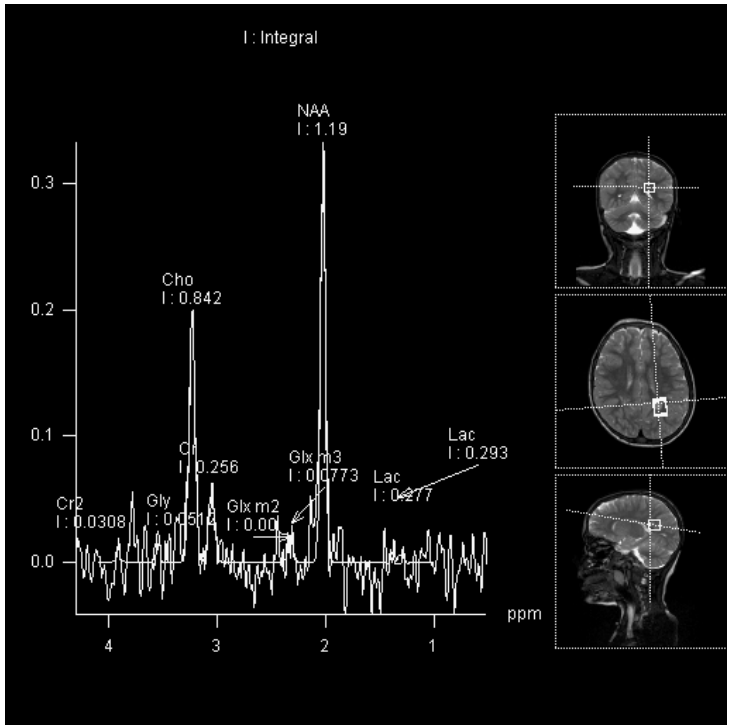
- Growth retardation
- Reduced muscle mass
- Facial dysmorphism
- Extrapyramidal movement disorder
- Mitochondrial myopathy (Anselm 2006)
- Progr neurol & psychiatric deterioration
  in 2 adults, intestinal obstruction (Kleefstra 2005)

CRTR case report

- 9 y female
- 3y: speech delay, seizures therapy resistant
- 5y:70-100/d complex parital
  - Eye rolling, holding breath, loss tone, stiffness
  - 5-45 s
  - EEG multifocal spikes, slow theta delta activity

CTRT case report cont

- MRS low cerebral creatine
- Urinary and CSF GAA normal
- SLC6A8, exon7 pGly356Val
- 50% reduced creatine uptake in fibroblasts
- Mother, sister are also affected, MR phenotype



CRTR case report cont

Creatine 400 mg / kg	Seizure free after 3 w Relaps after 3w No change with different dosing regimens No increase of cerebral creatine
Creatine 400 mg / kg Arginine 400 mg / kg Glycine 400 mg / kg	Significant improvement of seizures and EEG after 3 months Cerebral creatine pending

Combined substitution: new treatment option?

CDS: Principles of treatment

	Correction of deficiency	***Correction of accumulation***	***Alternative***
GAMT	Creatine supplement.	Arginine reduction	Ornitihine supplement
AGAT	Creatine supplement.	----------	----------
CRTR	Creatine& Arg&Gly?	----------	To be developed

CDS: Outcome of treatment

- GAMT Deficiency:
  - Improvement of epilepsy >> EPM
  - No improvement of MR
  - Early treatment?
- AGAT Deficiency:
  - Improvement of dev delay
  - Catch up / normal development after early treatment
- CRTR Deficiency:
  - Treatment response in heterozygous females?

CDS:
Questions & Challenges

- Frequency ?
- Improvement of treatment (GAMT, CRTR)?
- Prevention of neurologic sequelae by presymptomatic treatment (newborn screening)?
- Clinical heterogeneity, understanding of natural history
- Careful (standardised) documentation, objective measures for clinical severity
- Registry / Database

CDS: Biochemical Features

	Brain creatine Proton MRS	Guanidino acetate U /P /CSF	Creatinine 24 h urine U	U-Creatine / creatinine U
GAMT	↓↓	↑↑	↓	-
AGAT	↓↓	↓↓	(↓)	-
CRTR	↓↓	normal	(↓)	↑