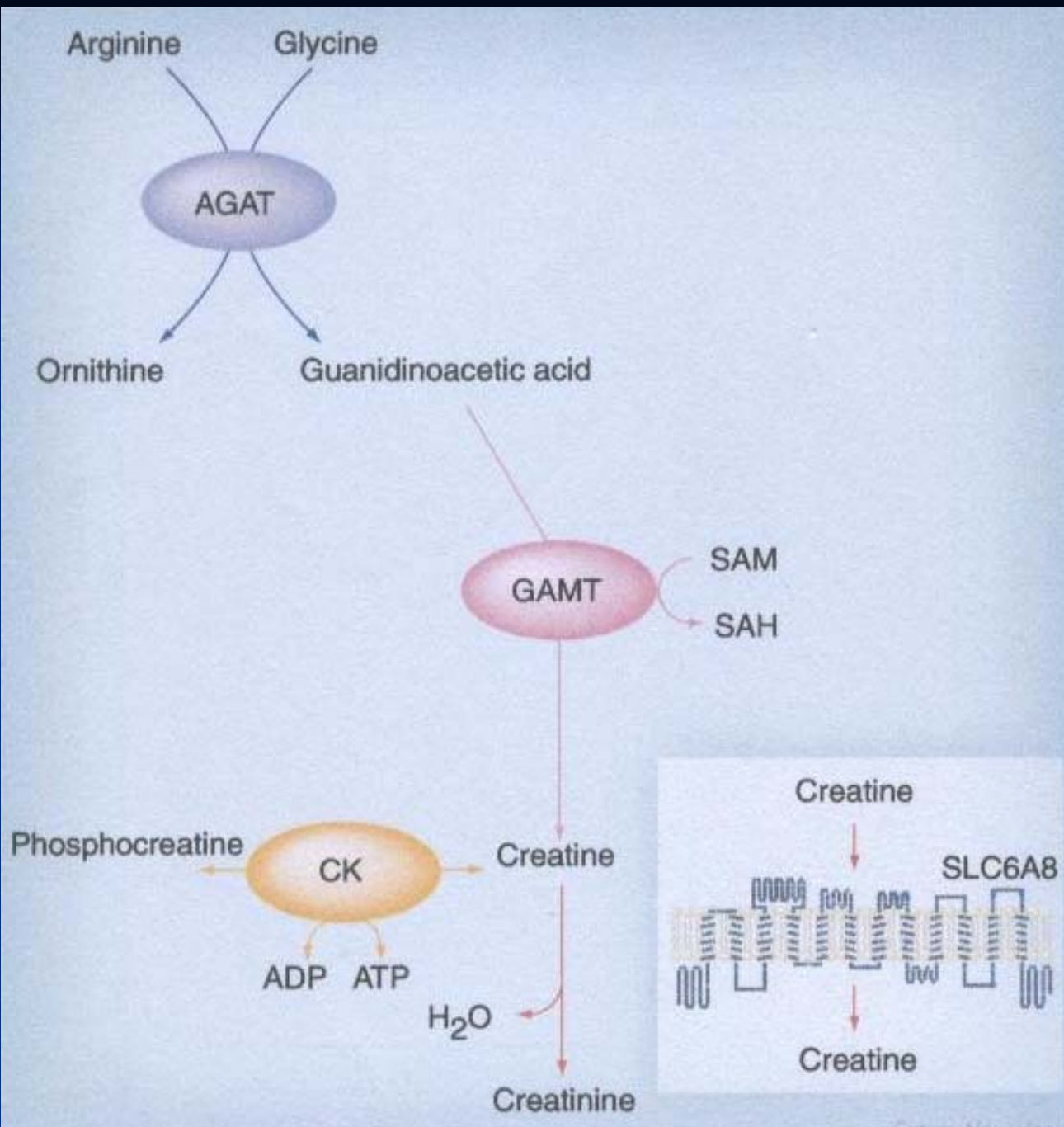




**WORKSHOP
I DIFETTI DEL
METABOLISMO DELLA
CREATINA**
Reggio Emilia, 8 Novembre 2008

Diagnosi differenziale clinica ed elementi caratterizzanti

D. Frattini, E. Della Giustina
Neuropsichiatria Infantile, ASMN, Reggio Emilia



AGAT

GAMT

SLC6A8

Sindromi da deficit cerebrale di creatina

| | AGAT (5) | GAMT (30) | SLC6A8 (28) ^o |
|------------------------------|-----------|---|--|
| DATI CLINICI | | | |
| Età alla diagnosi | 0-5 | 0-29 (esordio 3 m – 3 y) | 2-66 |
| Ritardo psicomotorio | 5/5 | 28/30 | 28/28 |
| Ritardo linguaggio | 5/5 | 22/30 | 28/28 |
| Ritardo mentale | 5/5 | 28/30 | 28/28 |
| Ipotonia | 2/5 | 27/30 | 14/19 |
| Disturbo comportamento | 1/5 | 22/30 (iperattivo/autistico/autoaggress.) | 17/22 (iperattività, autismo) |
| Disturbo movimento | NR | 15/30 | 10/22 |
| Epilessia | NR (1 CF) | 26/30 (9 Drug R) | 19/28 |
| Fenotipo lieve | NA | 3/30 | NA |
| Fenotipo medio | NA | 13/30 | NA |
| Fenotipo grave | NA | 12/30 | NA |
| ↓ o – Cr in H-MRS | 5/5 | 28/30 | 16/16 |
| MRI | n.n. | 6/23 alt glob pall (4 + sint extrapir) 17/23 n.n. o rit. miel. | n.n., alterazioni SB perivent ippocampo (sclerosi mesiale), evoluzione verso atrofica (cortico/cereb)? |
| DATI BIOCHIMICI | | | |
| creatina:creatinina urinario | | | ↑ 21/21 |
| GAA urinario | ↓ 5/5 | ↑ 30/30 | ↑ 2/4 |
| GAA plasmatico | ↓ 5/5 | ↑ 29/29 | ↑ 1/2 |
| Creatina plasmatica | ↓ 5/5 | ↓ 29/29 | NR |

D.D. ma.....

**ANCORA POCHI I CASI DESCRITTI (AGAT)
SEGNI E SINTOMI COMUNI**

- **EPILESSIA**
- **DISTURBI COMPORTAMENTALI**
- **DISTURBI DEL MOVIMENTO + ALT. N. PALLIDI**

SINTOMI CHE SI RISCONTRANO, SOLI O IN ASSOCIAZIONE, ANCHE IN ALTRI

**ERRORI CONGENITI DEL
METABOLISMO**

- **RITARDO MENTALE X LINKED**

| | | |
|--------------|---------------------|-----------------------------|
| AGAT (5) | GAMT (30) | SLC6A8 (28) ^o |
| NR (1 CF) | 26/30 (9 Drug R) | 19/28 |

Epilessia

Difetto di GAMT

Esordio: early onset (3 mesi – 2 anni) (talora anticipate da CF)

Semeiologia: T-C generalizzate, drop attack, crisi miocloniche, crisi T con apnea, assenze, assenze miocloniche, head drop

EEG: anomalie del fondo, anomalie focali, multifocali e generalizzate (P, PO, POL)

Farmaco resistenza: 9/26

| AGAT (5) | GAMT (30) | SLC6A8 (28) ^o |
|--------------|---------------------|-----------------------------|
| NR (1 CF) | 26/30 (9 Drug R) | 19/28 |

Epilessia

Difetto di SLC6A8

Esordio: tra i 2 e gli 8 anni (in 3 casi con SE all'esordio)

Semeiologia: CF, P, PC, PSG, generalizzata

EEG: anomalie focali, multifocali e generalizzate

Crisi poco frequenti e solitamente responsive ad AED ma descritti casi severi farmaco R (Mancardi, 2007)

Epilepsy in inborn errors of metabolism

Nicole I. Wolf¹, Thomas Bast¹, Robert Surtees²

¹ Department of Paediatric Neurology, University Children's Hospital Heidelberg, Germany

² Neurosciences Unit, Institute of Child Health, University College London, UK

Table 2. Classification of epilepsies of metabolic origin according to age at onset.

| | |
|------------------------|--|
| Neonatal period | Hypoglycaemia, pyridoxine-dependency, PNPO deficiency, nonketotic hyperglycinaemia, organic acidurias, urea cycle defects, neonatal adrenoleukodystrophy, Zellweger syndrome, folinic acid-responsive seizures, holocarboxylase synthase deficiency, molybdenum cofactor deficiency, sulphite oxidase deficiency |
| Infancy | Hypoglycaemia, GLUT1-deficiency, <u>creatine deficiency</u> , biotinidase deficiency, amino acidopathies, organic acidurias, congenital disorders of glycosylation, pyridoxine dependency, infantile form of neuronal ceroid lipofuscinosis (NCL1) |
| Toddlers | Late infantile form of neuronal ceroid lipofuscinosis (NCL2), mitochondrial disorders including Alpers' disease, lysosomal storage disorders |
| School age | Mitochondrial disorders, juvenile form of neuronal ceroid lipofuscinosis (NCL3), progressive myoclonus epilepsies |

Epilessia

Criteri di inclusione per d.d.:

1. Età di esordio: infanzia
2. Alcune trattabili (supplementazione, dieta)
3. Meno note / varianti atipiche
4. Condizioni prive di elementi diagnostici specifici e caratteristici



- ✓ Difetto di GLUT-1 (De Vivo, 2007)
- ✓ Difetto di biotinidasi (Grünewald, 2004)
- ✓ Aminoacidopatie (difetto sintesi di serina, ipergliciniemia non chetotica late onset (Leuzzi, 1990), MSUD scompensata, PKU non trattata)
- ✓ Organicoacidurie
- ✓ Piridossina dipendenza (variante atipica)
- ✓ CDG senza interessamento multisistemico (ipotonia, rit.psicomot., epilessia)
(I-c (Marquardt, 2003), I-d (Rimella, 2008))

| | Esordio | S. esordio | Semiologia | EEG | Elementi distintivi |
|---|-----------------------------|---|--|---|--|
| GLUT-1 KD | Entro 1° anno (2-6 m) | <u>Epilessia</u> FR, rit. psicomotorio, ipotonia, microcefalia (2°), atassia, distonia | T-C, assenze, assenze atipiche, miocloniche, mioclono-astatiche, con cianosi | F e generalizzate a tipo PO | Peggioramento sintomi in digiuno Ipoglicorrachia |
| Difetto di biotinidasi Biotina | 1-12 mesi | <u>Epilessia</u> FR, rit. psicomotorio, ipotonia, ± dist. comportamentali ± atassia ± atrofia ottica ± sordità | Miocloniche, toniche, spasmi | Attività lenta, anomalie parossistiche aspecifiche | Alopecia, dermatite, erosioni periorali (70%) ↑ lattato sangue e liquor Ac. Organici: spt ↑ 3 idrossi isovalerico MRI: alt. SB (rit.miel. ed leucoencefalopt. se non trattati) |
| Aminoacidopatie | | | | | |
| Deficit 3 fosfo-glicerato DH Serina | Primi mesi di vita | Microcefalia, ritardo psicomotorio, epilessia | T-C generalizzate, spasmi | Alterazioni ritmo di fondo, multifocali, S-B | Microcefalia alla nascita (alcuni casi secondaria (Hausler, 2001)) ↓ serina plasma e liquor |
| Iperglicinemica non chetotica (late onset) Dieta, imipramina (Wiltshire, 2000), benzoato, destrometorfano? | Entro anno | Epilessia, rit. psicomotorio, atassia, coreo-atetosi, dist. comportamentali | crisi T, spasmi | Multifocale, S-B | Possibile S-B in EEG ↑ CSF/plasma di glicina |
| Organicoacidurie | | | | | |
| 2 metil 3 idrossi butirrico aciduria Restriz. isoleucina? | Primi mesi- 6 anni | Regressione, coreoatetosi, epilessia ± deficit visivo/uditivo | Crisi T e miocloniche | Alterazioni del fondo, anomalie focli e multifocali | X-linked, ↑ lattato sangue e liquor (non in tutti) Ac. Organici: ↑ 2-Met-3-OH- butirrico e tiglilglicina |
| Aciduria metilmalonica con iperomocisteinemia B12 | Entro l'anno | Ritardo psicomotorio ipotonia, epilessia | Crisi P e generalizzate | Alterazioni focali e diffuse | Possibile an. Megalopbalstica |
| Piridossina dipendenza (variante atipica) B6 | 0-2 anni | Svil.n.n. prima di crisi, poi epilessia e successivo (se non trattato) ritardo psicomotorio, atassia, iperattività, corea MRI all'esordio: n.n. | T-C, C, parziali, spasmi, mioclonie, atoniche, T. Tendono a diventare sempre + frequenti e farmaco R | Anomalie focali (P T-FC) e generalizzate (PL) | Noise-Startle, iperattività prime delle crisi (alcuni casi) |

| AGAT (5) | GAMT (30) | SLC6A8 (28) ^o |
|----------|--|-------------------------------------|
| 1/5 | 22/30 (iperattivo/ autistico/auto aggress.) | 17/22 (iperattività, autismo) |

Disturbi comportamentali

Difetto di GAMT

Autismo, iperattività, auto-aggressività

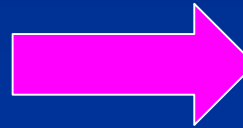
Difetto di SLC6A8

Iperattività, deficit di attenzione, autismo

Autism and Metabolic Diseases

Barbara Manzi, MD,* Anna Livia Loizzo, MD,* Grazia Giana, MD,
 and Paolo Curatolo, MD

| Disorder | Onset | Clinical Characteristics |
|--|----------------|---|
| Phenylketonuria | Neonatal | Autism, severe mental retardation, seizures (in untreated patient) |
| Adenylosuccinase deficit | First year | Autistic phenotype, psychomotor retardation, epilepsy |
| Creatine deficiency (guanidinoacetate methyltransferase deficiency, arginine-glycine amidinotransferase deficiency, transmembrane creatine transport deficiency) | 3 mo-2 y | Autistic phenotype, mental retardation, speech delay, epilepsy, extrapyramidal symptoms and signs |
| Inborn errors of cholesterol biosynthesis (variant of Smith-Lemli-Opitz syndrome) | After infancy | Autism, psychomotor retardation, poor expressive language, behavioral abnormalities |
| Biotinidase deficiency | 3-12 mo | Autism, ataxia, seizure, hypotonia, skin rash, alopecia, vision problems, hearing loss, organic academia |
| Infantile ceroid lipofuscinosis | ≥ 2 y | Autistic phenotype; regressed milestones; seizures; myoclonus; choreiform movements; visual loss; ataxia |
| Sanfilippo syndrome | During first y | Autistic phenotype; severe mental retardation; hyperactivity |
| Histidinemia ^{16,17} | Birth | Risk factor for the development of autism. Mental retardation, speech disturbances, many asymptomatic patients |
| Succinic semialdehyde dehydrogenase deficiency ¹⁸ | ≥ 3 mo | Autism or pervasive developmental disorder, delayed motor, intellectual; speech and language development. Nonspecific phenotypic presentation |
| Dihydropyrimidine dehydrogenase deficiency ^{19,20} | ≤ 1 y | Autism; seizures; motor and mental retardation; ocular abnormalities; growth retardation; microcephaly; asymptomatic individuals |



80 % dei casi: causa sconosciuta (Manzi, 2008)

IEM < 5 % dei casi (Rutter, 1997)

| | Esordio | S. clinici | S. distintivi | MR |
|---|--------------------|--|--|--|
| Difetto di biotinidasi | 3-12 mesi | Rit. Psicomotorio, ipotonia, Epilessia FR, AUTISMO Successivamente: atassia, atrofia ottica, sordità | Alopecia, dermatite, erosioni periorali (70%) ↑ lattato sangue e liquor Ac. Organici: spt ↑ 3 idrossi isovalerico MRI: alt. SB (rit.miel. ed leucoencefalopt. se non trattati) | Segnalati: atrofia, ↑ dimensioni VL |
| Deficit di andenilosuccinasi (sintesi purine) | Primi mesi di vita | AUTISMO (50%), Ritardo psicomotorio, ipotonia, epilessia ± scarso accrescimento, ± ipotrofia muscolare | Succinil aminoamidazolo Succinil adenosina, Carboxamide riboside in urina e liquor | Inizialmente normale, poi ridotta mielinizzazione, anomalie SB, ipoplasia/trofia cervelletto (verme) |
| Difetto di di-idropirimidina deidrogenasi (catabolismo pirimidine) | 1-3 anni | Ritardo mentale, epilessia, atassia, AUTISMO, anomalie oculari, microcefalia | GC/MS: aumento uracile , 5 OH metil uracile e timina | |
| Difetto di succinico semialdeide deidrogenasi (SSADH) | 20 m – 6 anni | Ritardo psicomotorio, mentale, atassia/ <u>distonia</u> /corea/atetosi, ritardo del linguaggio, AUTISMO, crisi epilettiche occasionali (50%) | Acido 4 OH butirrico in urine | n.n. o aumento di segnale dei globi pallidi |

| | | |
|----------|-----------|--------------------------|
| AGAT (5) | GAMT (30) | SLC6A8 (28) ^o |
| NR | 15/30 | 10/22 |

Disturbi del movimento con alterazione n.pallidi

Difetto di GAMT

corea, atetosi, atassia (talora + componenti piramidali) ed emiballismo

6/23 alt glob pall (4 + sint extrapir)

Difetto di trasportatore

coreoatetosi, distonia

TABLE 3-7

ANATOMIC DISTRIBUTION OF SOME DISEASES AFFECTING BASAL GANGLIA

| Diagnosis | Globus Pallidus | Caudate | Putamen | White Matter |
|---|-----------------|---------|---------|--------------|
| Acute | | | | |
| Hypoxia/ischemia—neonate | + | - | + | +/- |
| Hypoxia/ischemia—older child | + | ++ | ++ | + |
| Hypoglycemia—neonate | +/- | - | - | ++ |
| Hypoglycemia—older child | +/- | + | + | + |
| Cyanide intoxication | ++ | - | - | - |
| Carbon monoxide intoxication | ++ | + | + | + |
| Hemolytic-uremic syndrome | + | + | + | + |
| Osmotic myelinolysis | + | + | + | + + pons |
| Encephalitis | + | + | + | + |
| Chronic | | | | |
| Leigh's syndrome | + | + | ++ | + |
| Canavan disease | ++ | - | - | ++ |
| GM ₂ Gangliosidosis | - | ++ | - | + |
| Juvenile Huntington Dz. | - | ++ | ++ | - |
| Wilson's disease | ++ | + | ++ | + |
| Glutaric aciduria type I | - | ++ | ++ | ++ |
| Glutaric aciduria type II | - | | + | + |
| Molybdenum cofactor def. | - | ++ | ++ | + |
| Methylmalonic acidemia | + | - | - | + |
| Pantothenate kinase associated neurodegeneration (Hallervorden-Spatz disease) | ++ | - | - | - |
| Propionic acidemia | | ++ | ++ | + |
| Succinic semialdehyde dehydrogenase deficiency | ++ | | | |
| <u>Guanidinoacetate methyltransferase deficiency</u> | ++ | | | |
| Isovaleric acidemia | ++ | | | |
| L-2-hydroxyglutaric aciduria | ++ | | | ++ |
| Chronic liver disease | ++ | | | |
| Huntington disease | + | ++ | ++ | + |
| Kearns-Sayre syndrome | ++ | - | - | ++ |

++, very frequent involvement; +, occasional involvement; -, lack of involvement.

| | Esordio | Clinica | Disturbo Movimento | Altre anomalie RM |
|--|--|--|---|---|
| Difetto di succinico semialdeide deidrogenasi (SSADH) | 20 m- 6 anni | ritardo psicomotorio, mentale, atassia / <u>distonia</u> /corea/atetosi, ritardo del linguaggio, autismo, crisi epilettiche occasionali | atassia, coreoatetosi | + n. alterazioni segnale n. dentati, cervelletto, atrofia verme |
| Pantotenato kinasi assoc. neurodegen. Forma classica | 0-6 anni | segni piramidali, demenza, retinopatia | distonia, corea, atetosi parkinsonismo | alt.sost nigra, eye of the tiger |
| Atipica | 7-20 anni | più lieve e meno progressiva | | |
| Acidemia isovalerica (forma cronica intermittente) | Prima infanzia | ritardo psicomotorio, ritardo mentale, episodi di scompenso (vomito, letargia, acidosi) in fase infettiva (successiva lesione pallidi) | | |
| Encefalopatia Bilirubinica (<u>anamnesi</u>) | Acuta neonatale Cronica/subtlte | letargia, difficoltà alimentazione, ipo/ipertono, opistotono, crisi convulsive, anomalie mov. oculari, BAEPs assenti o alterati. fenotipo clinico meno severo con anomalie neurologiche più lievi, sordità isolata. | distonia, atetosi, atassia (± segni piramidali) | iperintensità pallidi bilat. |

E nelle citopatie mitocondriali (Leigh, Leigh-like).....

SHORT REPORT

Guanidinoacetate methyltransferase deficiency masquerading as a mitochondrial encephalopathy

A. A. M. Morris · R. E. Appleton · B. Power · D. M. Isherwood · L. J. Abernethy ·
R. W. Taylor · D. M. Turnbull · N. M. Verhoeven · G. S. Salomons · C. Jakobs

deficiency is a rare disorder of creatine synthesis. We report a patient who presented at 10 months of age with hypotonia and global developmental delay. Subsequently, she developed seizures and choreoathetosis. Magnetic resonance imaging showed high signal bilaterally in the globus pallidus on T2-weighted images. Mitochondrial respiratory chain studies revealed low complex I activity (in muscle 0.052 nmol NADH

language. The occurrence of secondary respiratory chain abnormalities in GAMT deficiency may lead to misdiagnosis, particularly as the clinical and radiological features resemble those seen in mitochondrial encephalopathies. It is important to establish the correct diagnosis because specific treatment is available.

Ritardo mentale

NS-XLMR

In popolazione generale: 1%

(3% se incluso RM lieve) (Almeida, 2006)

In popolazione con RM: 5-12% legate a cromosoma X (Stevenson, 2000)

Fra-X: forma più frequente

Forme non sindromiche

Table 2

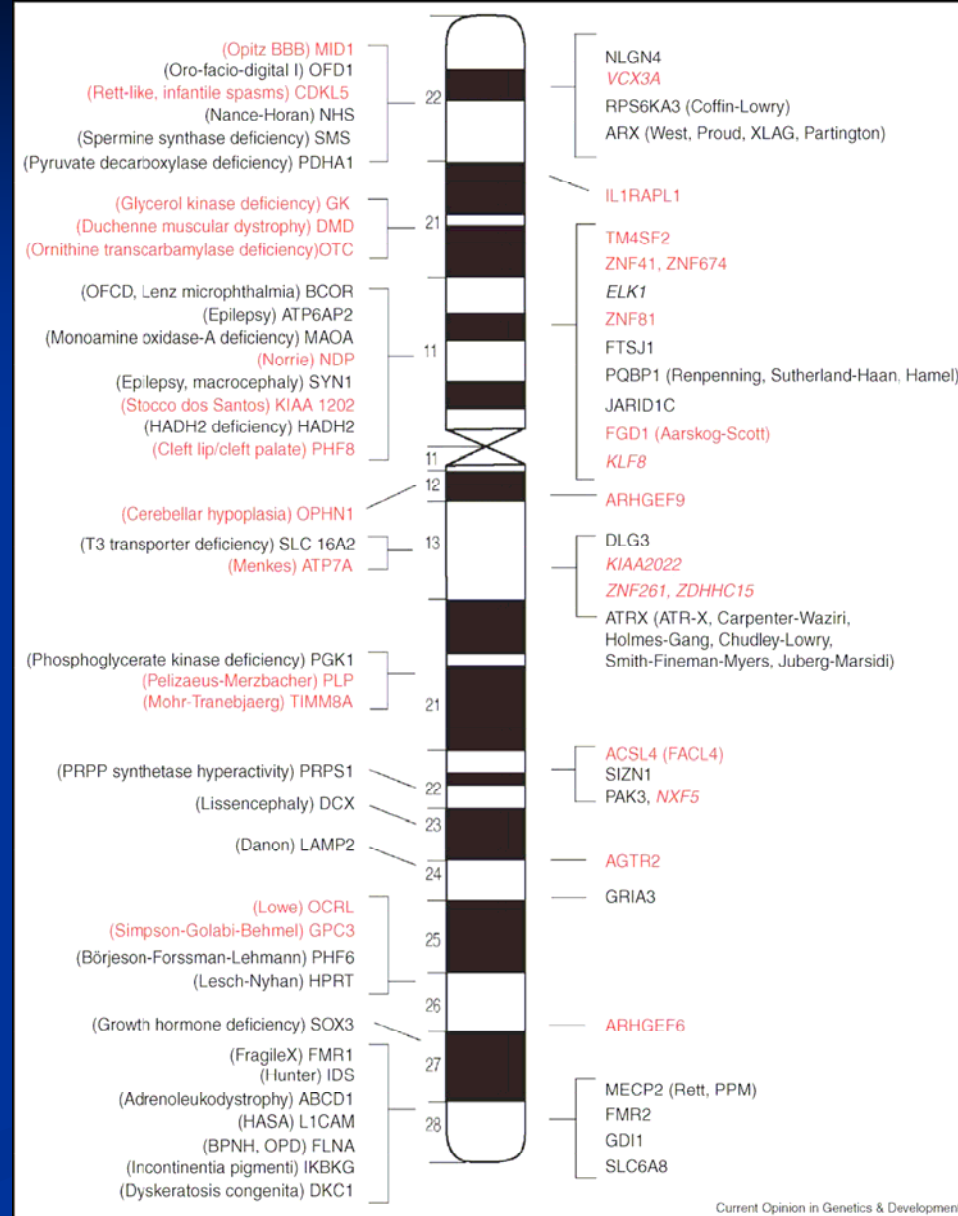
Estimated mutation frequencies in families with NS-XLMR.

| Gene symbol | % of families with mutations |
|---|------------------------------|
| ARX | >5 |
| JARID1C, <u>SLC6A8</u> | >2 |
| IL1RAPL1, PAK3, DLG3, FTSJ1 | 1-2 |
| ACSL4, GDI1, RSK2 ^a , GRIA3 | <1 |
| PQBP1 ^a , MECP2 ^{a,b} , ARHGGEF6, AGTR2 | Rare to very rare |
| All known genes | Up to 50% (?) |

Compiled from data of the EURO-MRX Consortium and other groups (P Tarpey *et al.*, unpublished; C Schwartz *et al.*, unpublished).

^a More common in syndromic XLMR.

^b Including gene duplications.



Current Opinion in Genetics & Development

| AGAT (5) | GAMT (30) | SLC6A8 (28) ^o |
|----------|-----------|--------------------------|
| 5/5 | 28/30 | 28/28 |

Ritardo mentale

November (1 of 2) 2006 NEUROLOGY 67 1713



High frequency of creatine deficiency syndromes in patients with unexplained mental retardation

L. Lion-François, MD; D. Cheillan, PhD; G. Pitelet, MD; C. Acquaviva-Bourdain, PhD; G. Bussy; F. Cotton, MD; L. Guibaud, PhD; D. Gérard, MD; C. Rivier, MD; C. Vianey-Saban, PhD; C. Jakobs, PhD; G.S. Salomons, PhD; and V. des Portes, PhD

Difetto di trasportatore

Ritardo mentale: lieve/moderato/severo

- Soggetti maschi con RM: 2.1% (2/95 Maricmek-Mahmutoglu 2007),
- Soggetti maschi con NS-XLMR: 2.1 % (6/288 Rosemberg 2004),
- Soggetti maschi - per fraX: 3.5% (4/114 Lion-Francois, 2006)

INCIDENZA di difetto di trasportatore in popolazione generale con RM senza causa nota: 0.2 % (Almeida, 2006)

The ARX story (epilepsy, mental retardation, autism, and cerebral malformations): one gene leads to many phenotypes

Elliott H. Sherr

Partington syndrome
(mental retardation,
ataxia, and dystonia)

Table 1. Spectrum of ARX mutations

| Mutation | Protein alteration | Clinical presentation |
|--------------|--------------------------|----------------------------|
| c.420-451del | Pre-HmD truncation | XLAG |
| c.790delC | Pre-HmD truncation | XLAG |
| p.R332H | HmD missense | XLAG |
| c.1117C>T | HmD truncation | XLAG |
| c.1188T>C | HmD truncation | XLAG |
| c.1372delC | Post-HmD truncation | XLAG |
| p.L343Q | HmD missense | XLAG |
| p.R332C | HmD missense | XLAG |
| p.790delC | Pre-HmD truncation | XLAG |
| c.428-451dup | Polyalanine expansion | MRX, dystonia, brain cysts |
| p.L33P | Non-HmD missense | MRX |
| c.428-451dup | Polyalanine expansion | MRX |
| c.428-451dup | Polyalanine expansion | MRX |
| c.428-451dup | Polyalanine expansion | MRX |
| c.428-451dup | Polyalanine expansion | MRX |
| c.428-451dup | Polyalanine expansion | MRX |
| c.304ins6 | Polyalanine exp (2 a.a.) | MRX |
| p.Q163R | Non-HmD substitution | MRX |
| p.G286S | Non-HmD substitution | MRX |
| c.428-451dup | Polyalanine expansion | Partington syndrome |
| c.428-451dup | Polyalanine expansion | ISSX |
| c.428-451dup | Polyalanine expansion | MRXS |
| c.428-451dup | Polyalanine expansion | Parting syndrome |
| c.428-451dup | Polyalanine expansion | Parting syndrome |
| p.P353L | HmD missense | XMESID |
| Genomic del | C-terminal truncation | ISSX/WS |
| c.333ins21 | Polyalanine expansion | ISSX/WS |
| c.333ins21 | Polyalanine expansion | ISSX/WS |
| c.428-451dup | Polyalanine expansion | ISSX/WS |

Brain Dev. 2008 (ahead of print)

Expansion of the first polyalanine tract of the ARX gene in a boy presenting with generalized dystonia in the absence of infantile spasms.

Shinozaki Y, Osawa M, Sakuma H, Komaki H, Nakagawa E, Sugai K, Sasaki M, Goto Y.

Department of Child Neurology, National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira 187-8551, Japan.

mental
retardation,
tonic seizures
dystonia no IS

Deficit secondari di creatina

Lesionali

ipossia/ischemia del neonato,
neurotrauma cranico

Metabolici

atrofia girata della retina

difetti di GLUT1

citopatia mitocondriale

patologia degenerativa della sostanza bianca

RUOLO
DELLA
CREATINA?

Creatina in SNC in via di sviluppo

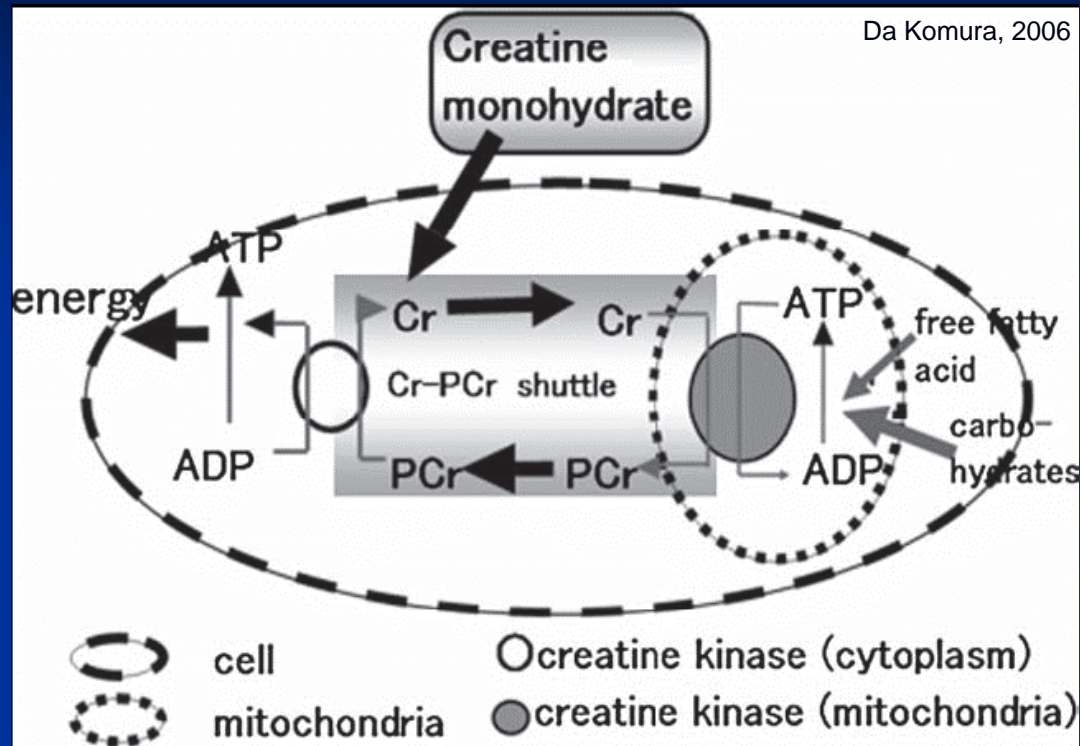
The Journal of Neuroscience, November 15, 2002, 22(22):9810–9820

Ammonium-Induced Impairment of Axonal Growth Is Prevented through Glial Creatine

Olivier Braissant,^{1*} Hugues Henry,^{1*} Anne-Marie Villard,¹ Marie-Gabrielle Zurich,² Marc Loup,¹ Barbara Eilers,¹ Gianni Parlascino,¹ Edouard Matter,¹ Olivier Boulat,¹ Paul Honegger,² and Claude Bachmann¹

¹Clinical Chemistry Laboratory, University Hospital, CH-1011 Lausanne, Switzerland, and ²Institute of Physiology, University of Lausanne, CH-1005 Lausanne, Switzerland

Creatina – Ruolo Energetico



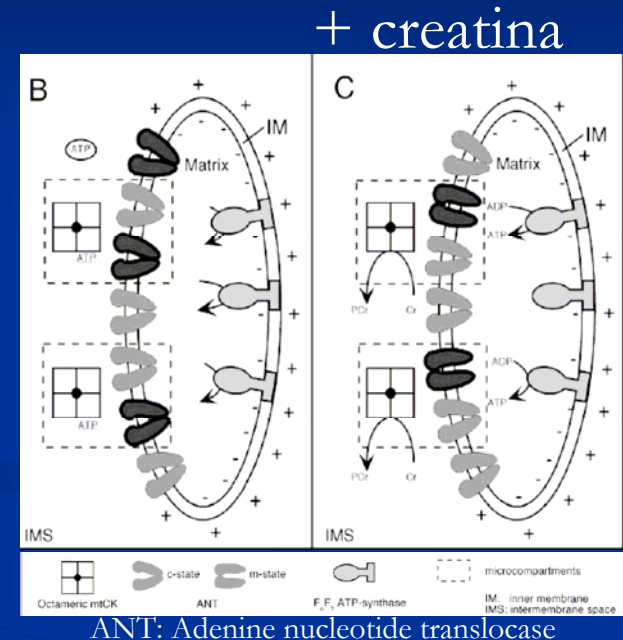
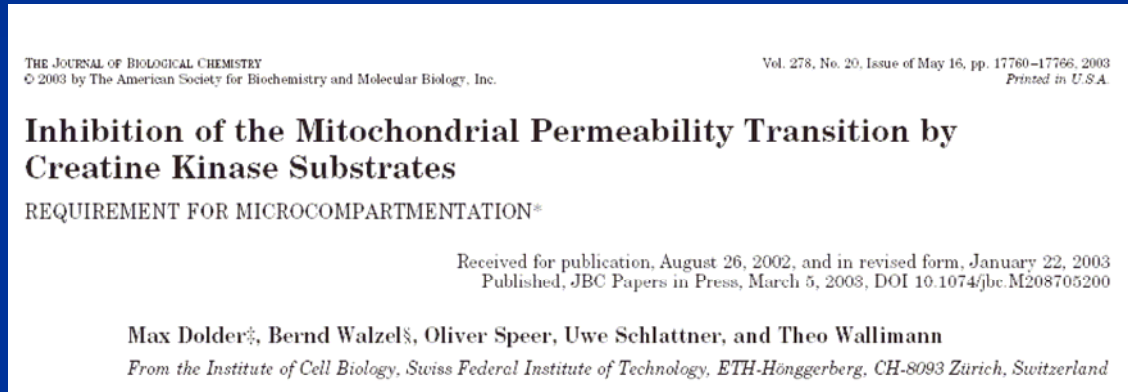
- “shuttle” tra citosol e mitocondri dove $Cr > CrP$ da CK mitocondriale (ATP)
- CrP mediante CK citosolica: $ADP > ATP$
- CrP agisce anche come fonte energetica immediatamente disponibile e può agire come fonte di P inorganici per attivazione glicolisi/glicogenesi

Creatina – Neuroprotettore?

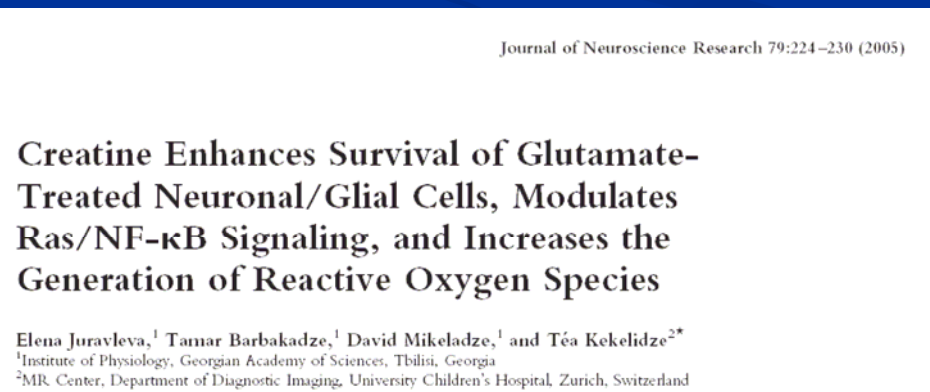
Effetto protettivo su sopravvivenza neuronale riducendo morte neuronale eccitotossica (colture neuronali esposte ad alte concentrazioni di glutammato) (Brewer & Wallimann, 2000)

Come?

- Modulando la permeabilità mitocondriale



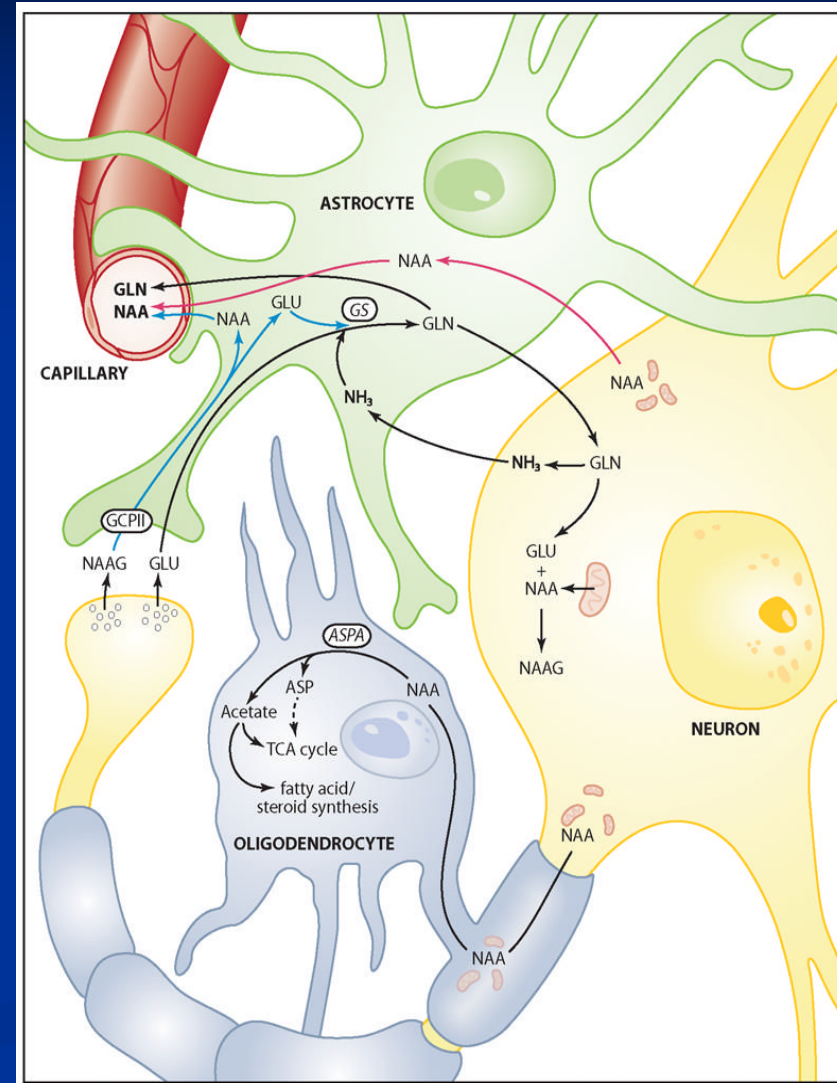
- Intervenendo sul segnale intracellulare di apoptosi



Hp Creatina/ N-acetilaspato in Spettroscopia

- 1) NAA: marker di integrità neuronale
- 2) NAA: in oligodendrociti ruolo in formazione mielina e lipidi costituenti
- 3) NAA: perciò, può essere marker dello stato della sostanza bianca e fz mitocondriale (dove si trova)

In patologie con difetto di NAA e caduta del picco in spettroscopia > ricaduta negativa su sistema CR/PCr/CK > ritorna negativamente sul NAA e sue funzioni di mantenimento di sostanza grigia e bianca



ORIGINAL RESEARCH

Classification of Childhood White Matter Disorders Using Proton MR Spectroscopic Imaging

A. Bizzi
G. Castelli
M. Bugiani
P.B. Barker
E.H. Herskovits
U. Danesi
A. Erbetta
I. Moroni
L. Farina
G. Uziel

BACKGROUND AND PURPOSE: Childhood white matter disorders often show similar MR imaging signal intensity changes, despite different underlying pathophysiologies. The purpose of this study was to determine if proton MR spectroscopic imaging (¹H-MRSI) may help identify tissue pathophysiology in patients with leukoencephalopathies.

MATERIALS AND METHODS: Seventy patients (mean age, 6; range, 0.66–17 years) were prospectively examined by ¹H-MRSI; a diagnosis of leukoencephalopathy due to known genetic defects leading to lack of formation, breakdown of myelin, or loss of white matter tissue attenuation (rarefaction) was made in 47 patients. The diagnosis remained undefined (UL) in 23 patients. Patients with definite diagnoses were assigned (on the basis of known pathophysiology) to 3 groups corresponding to hypomyelination, white matter rarefaction, and demyelination. Choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) signals from 6 white matter regions and their intra- and intervoxel (relative to gray matter) ratios were measured. Analysis of variance was performed by diagnosis and by pathophysiology group. Stepwise linear discriminant analysis was performed to construct a model to predict pathophysiology on the basis of ¹H-MRSI, and was applied to the UL group.

ORIGINAL RESEARCH ■ PEDIATRIC IMAGING

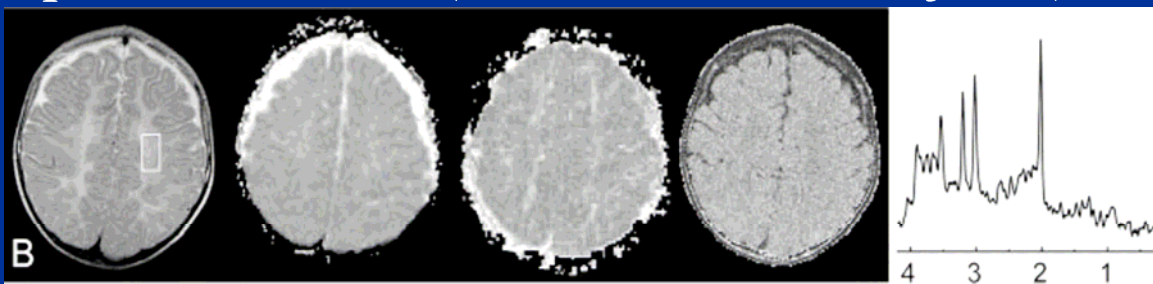
Childhood White Matter Disorders: Quantitative MR Imaging and Spectroscopy¹

Radiology

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Purpose: To prospectively investigate whether quantitative magnetic resonance (MR) parameters, including magnetization transfer ratio (MTR), apparent diffusion coefficient (ADC), fractional anisotropy (FA), and MR spectroscopic metabolite concentrations, allow for discrimination between different types of pathologic conditions that underlie signal intensity abnormalities in white matter.

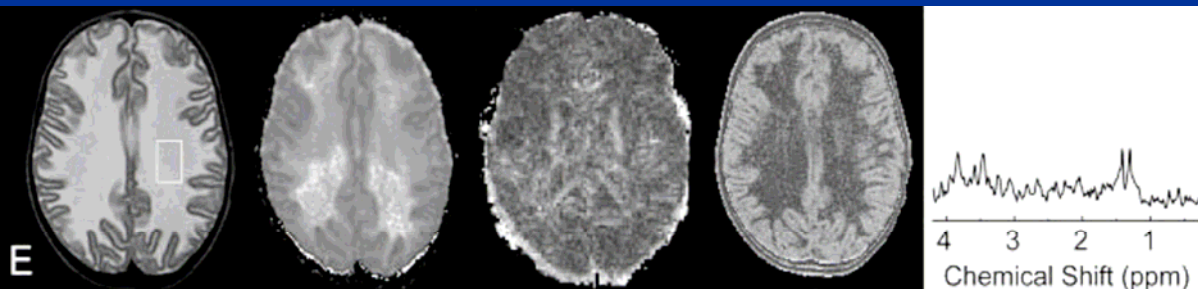
Ipomielinizzanti (Pel-Merz: PLP1, GJA12)



n. NAA, **n** o **↑** Cr

Quasi normale turnover membrane/densità assonale (anche se c'è deficit permanente di deposizione di mielina)

Demielinizzanti/rarefazione/cavitazione (Krabbe, Metacrom, LVWM, MLC, citop.mitoc.)

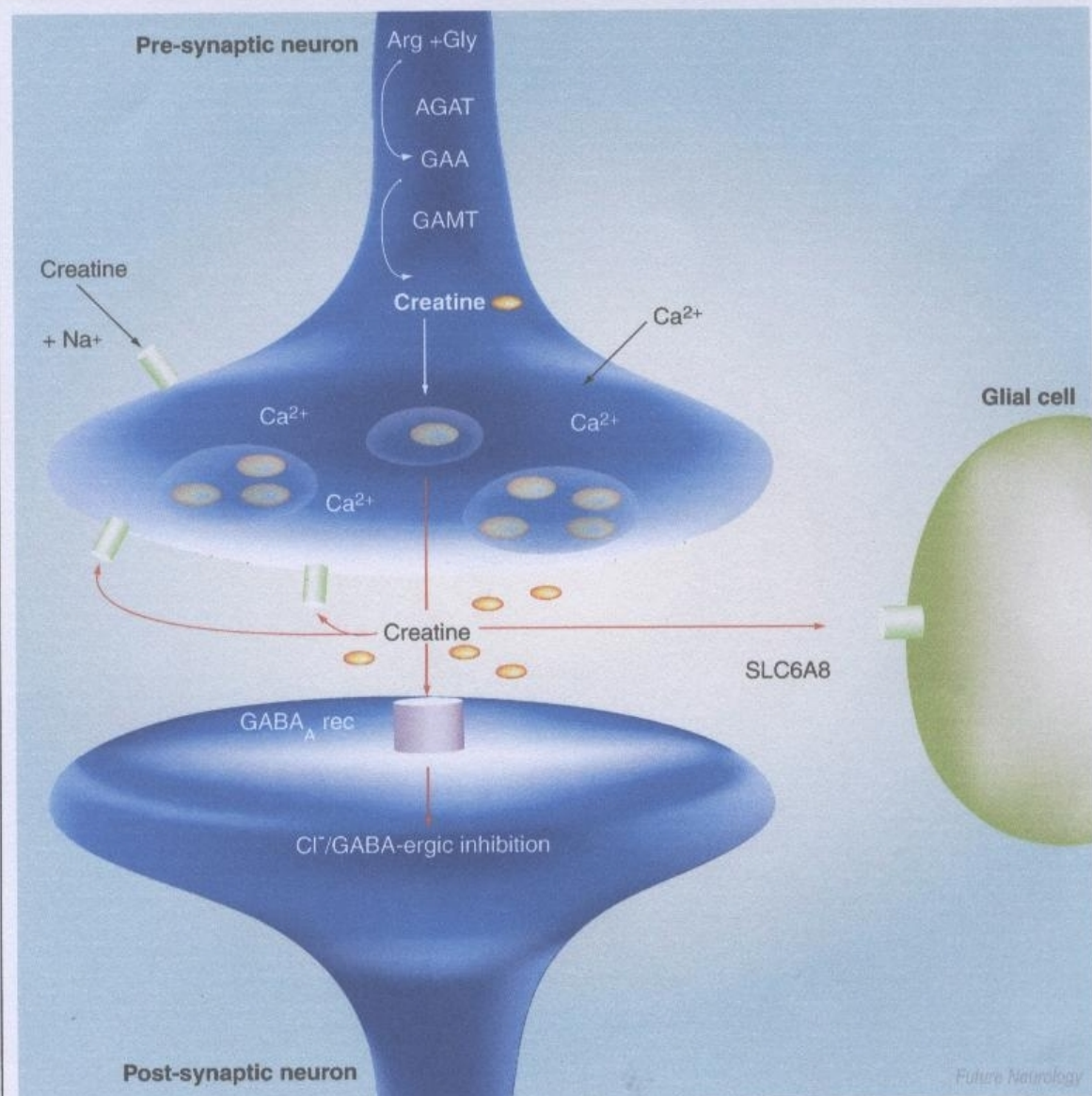


↓ NAA, **↓** Cr
(cho **↑** dem, **↓** cav)

Danno / perdita assonale + prolif. astroc.

Creatina – Neuromodulatore?

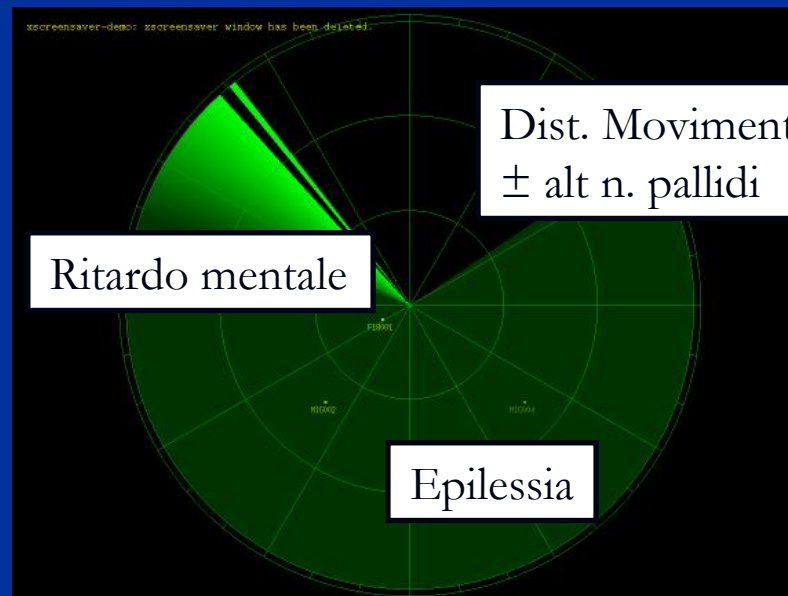
Figure 6. Proposed model of action for cerebral creatine.



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Are cerebral creatine deficiency syndromes on radar screen?

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GRAZIE