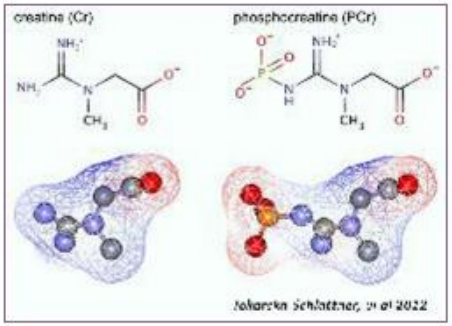
Hospital Pediátrico
C H U C

Doenças Hereditárias
do Metabolismo

XI Curso Básico



23 a 25 setembro 2013

CASA DA ACREDITAR

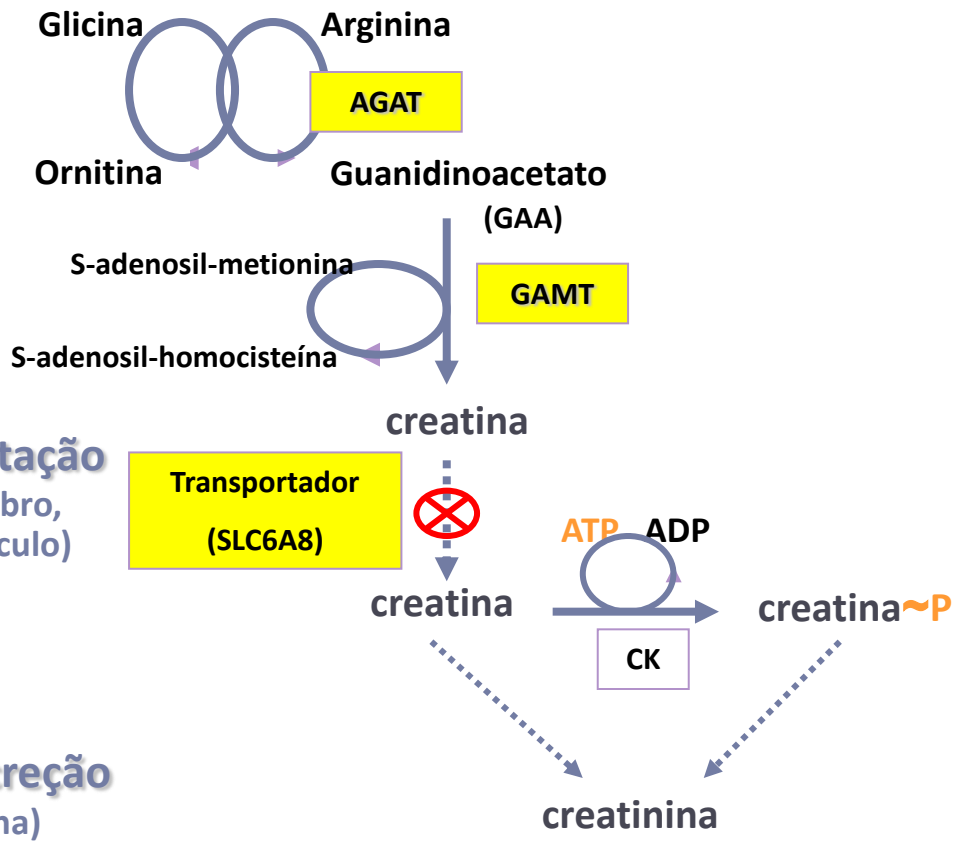
Hospital Pediátrico de Coimbra - CHUC

Défices de creatina cerebral

Carolina Duarte

Metabolismo da Creatina

Síntese
(rim ➔ fígado)



Défices de creatina cerebral

Grupo de doenças que cursam com alterações na **síntese** ou no **transporte** da creatina

3 doenças

défice de AGAT (arginina:glicina amidinotransferase)

défice de GAMT (guanidinoacetato metiltransferase)

→ AR

défice do transportador da creatina (SLC6A8) → lig X

em comum

↓↓ creatina cerebral

espetro fenotípico
- DI
- pert linguagem
- epilepsia ...

Défice de GAMT

Primeiro défice de creatina descrito (1994)

Genética: transmissão AR gene GAMT no Cr19p13.3; várias mutações, ++ c.327G>A e **c.59G>A**

Prevalência: atualmente são conhecidos mais de 50 casos

29 doentes (2007) » **10 portugueses**

9/10 mutação **c.59G>C** (8 homo/1 heterozigotia)

taxa portadores: 0,8% (>Arquipélagos e Porto)

Available online at www.sciencedirect.com
ScienceDirect
Molecular Genetics and Metabolism 91 (2007) 1–6
Molecular Genetics and Metabolism
www.elsevier.com/locate/ymgme

A prevalent pathogenic *GAMT* mutation (c.59G>C) in Portugal

L.S. Almeida [a,b], L. Vilarinho [b], P.S. Darmin [a], E.H. Rosenberg [a], C. Martinez-Muñoz [a], C. Jakobs [a], G.S. Salomons [a,*]

[a] *Department of Clinical Chemistry, Metabolic Unit, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands*
[b] *Instituto de Genética Médica Dr Jacinto Magalhães, Praça Pedro Nunes 88, 4099-028 Porto, Portugal*

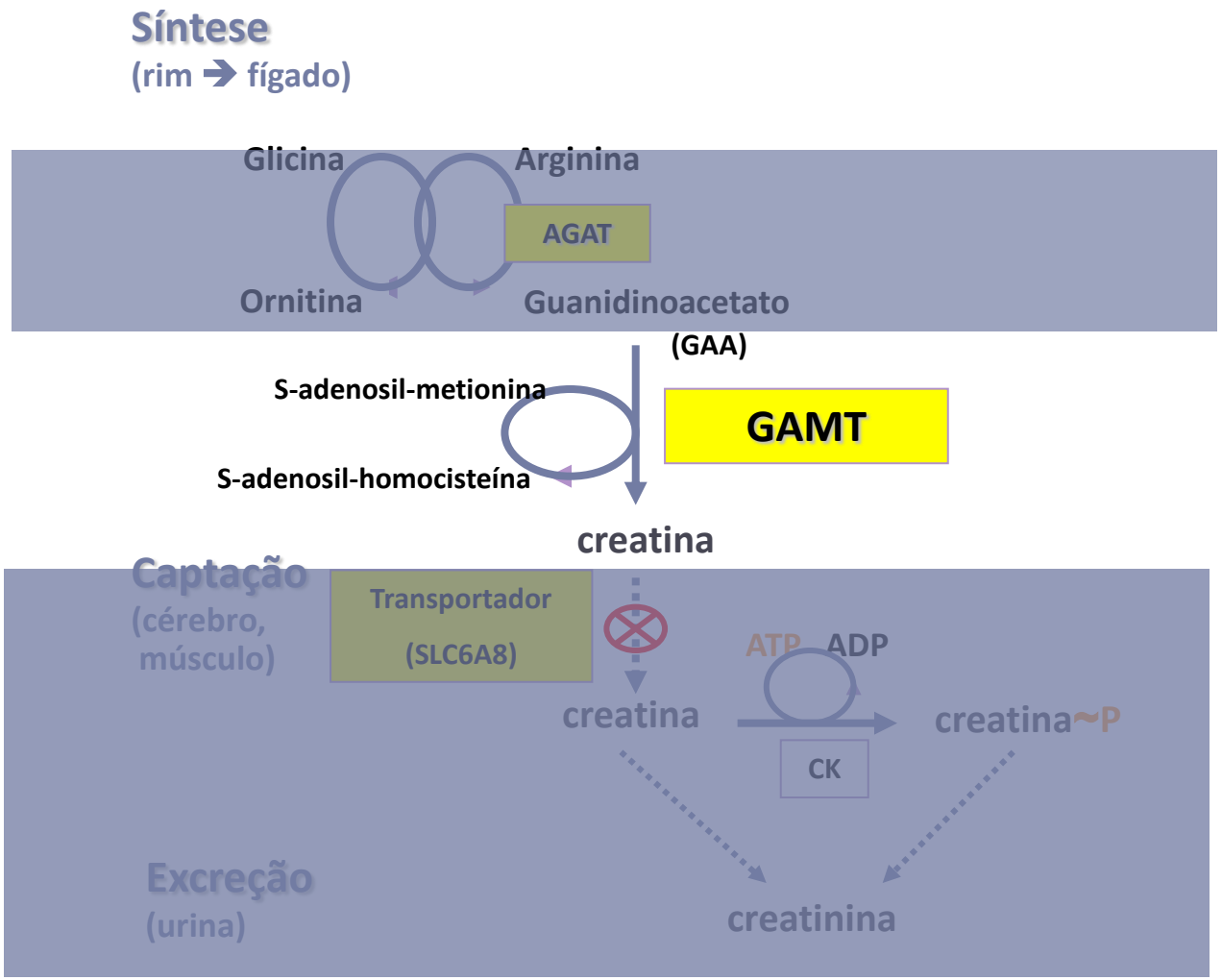
Received 12 October 2006; received in revised form 9 January 2007; accepted 10 January 2007
Available online 1 March 2007

Abstract

Guanidinoacetate methyltransferase (GAMT) deficiency (MIM 601240), an autosomal recessive disorder of creatine biosynthesis, presents with mental retardation, extrapyramidal symptoms, autistic-like behavior and epilepsy. Other hallmarks are cerebral creatine deficiency, increased levels of guanidinoacetate in body fluids and mutations in the *GAMT* gene. Creatine supplementation partially restores cerebral creatine content. Worldwide, 29 patients have been identified and 15 different mutations have been reported in the *GAMT* gene. Ten out of these 29 patients are of Portuguese origin. Likely, a founder effect and a high carrier rate in Portugal exist, since in 17 out of the 20 Portuguese alleles the c.59G>C; p.Trp20Ser mutation was found. We investigated the carrier rate of the c.59G>C; p.Trp20Ser mutation in different regions of Portugal and confirmed the pathogenic nature of this missense mutation by transient transfections. Anonymous bloodspots (1002) were screened for the presence of the c.59G>C; p.Trp20Ser mutation by SNaPshot (Single Nucleotide Polymorphism Multiplex Kit). Eight carriers of c.59G>C; p.Trp20Ser were detected of which four are derived from the Archipelagos. This suggests that the carrier rate of the c.59G>C; p.Trp20Ser mutation is relatively high in these islands, as well as in other parts of Portugal. It also implies that newborn screening in these regions is warranted for this treatable disorder.

Keywords: Creatine deficiency; GAMT; c.59G>C p.Trp20Ser; W20S; Carrier rate

Défice de GAMT



↓ Creatina cerebral
(reserva ATP, anti-oxidante, neuromodulação)

↑ GAA
(radicais livres, peroxidação lipídica, necrose neuronal)

Défice de GAMT

Heterogeneidade fenotípica, mas potencialmente mais grave

- défice intelectual ligeiro a severo, com ou sem autismo
- epilepsia de gravidade variável (desde ligeira a refratária à terapêutica)
- distúrbio progressivo do movimento/ alterações extrapiramidais

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY CASE REPORT

2009

Guanidinoacetate methyltransferase (GAMT) deficiency: late onset of movement disorder and preserved expressive language

DECLAN J O'ROURKE MRCPI[1] | STEPHANIE JAKOBS PHD[3] | AHMAD MONAVARI MRCPI

1 Department of Neurology, Children's University Hospital, Dublin, Clinical Chemistry, Metabolic Unit, VU University Medical Centre, A Dublin, Ireland.

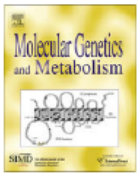
Correspondence to Dr Mary D King at Department of Neurology, C E-mail: mary.king@cuh.ie

Molecular Genetics and Metabolism 96 (2009) 38–43

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Expanded clinical and molecular spectrum of guanidinoacetate

8 casos apresentação heterogénea; idade de dg 0 - 14 anos

J Inherit Metab Dis (2007) 30:100
DOI 10.1007/s10545-006-0478-2

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

1 caso; clínica aos 10 meses; suspeita dça mitocondrial; dg aos 21 meses

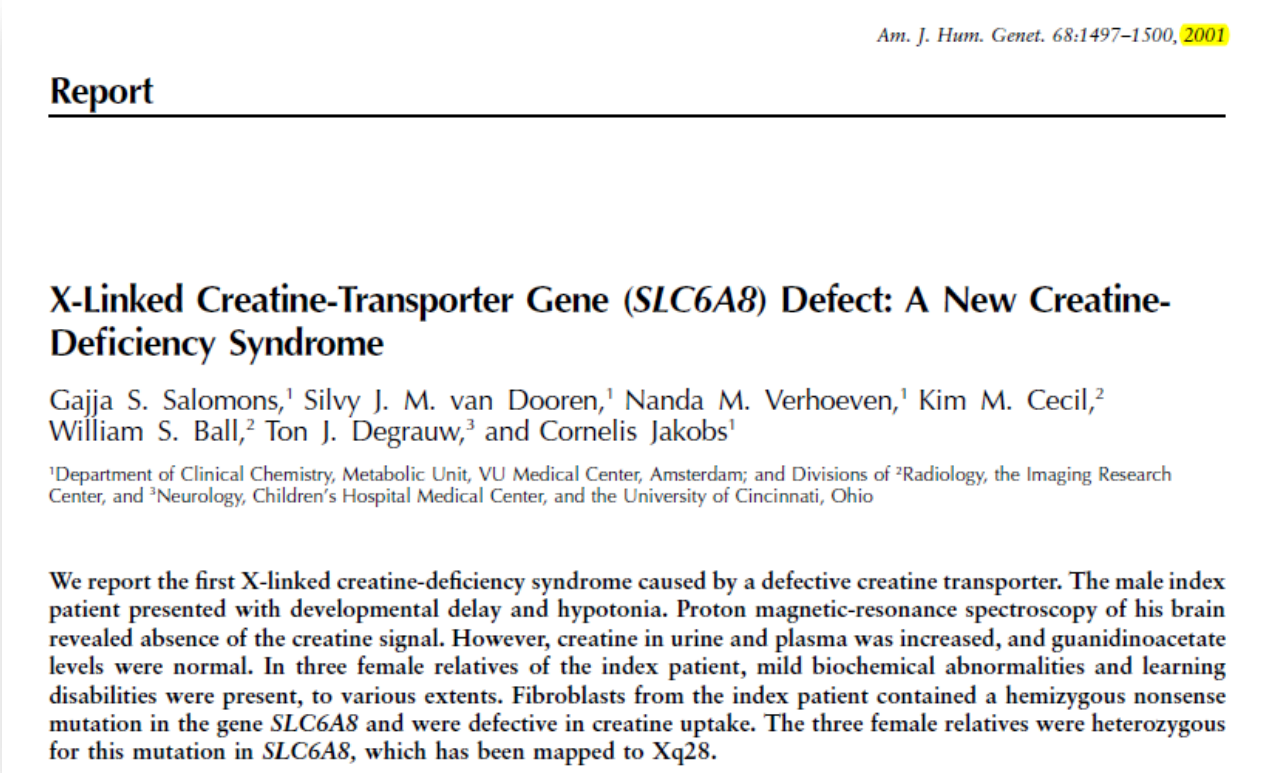
Défice do transportador da creatina

Descrito pela primeira vez em 2001 (caso com DI, autismo, ∅ linguagem)

Genética: gene SLC6A8, **Xq28**;

(36 mutações conhecidas; ++ c.319_321delCTT e c.1221_1223delTTC)

Prevalência: atualmente são conhecidos mais de 170 casos



Am. J. Hum. Genet. 68:1497–1500, 2001

Report

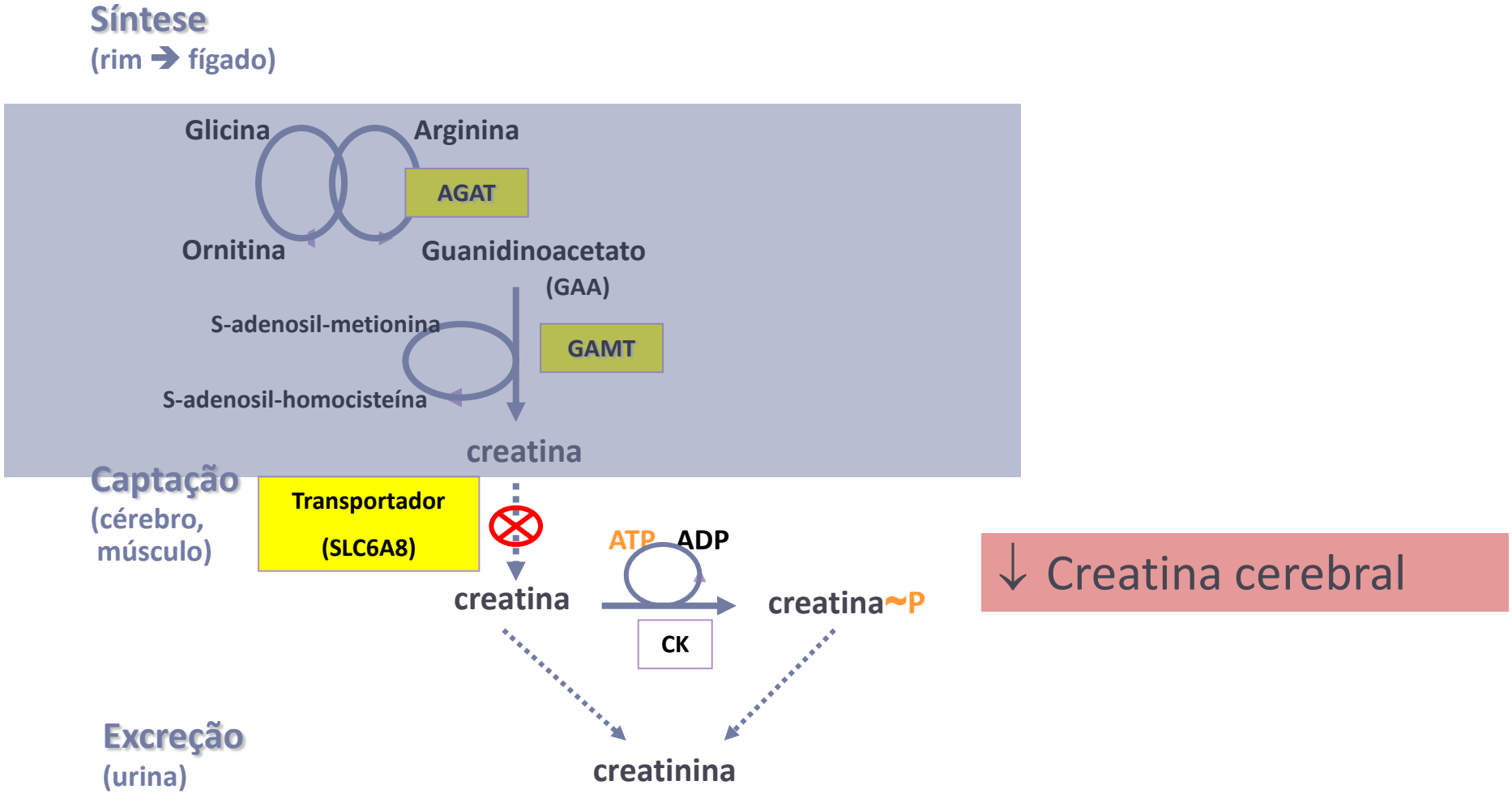
X-Linked Creatine-Transporter Gene (*SLC6A8*) Defect: A New Creatine-Deficiency Syndrome

Gajja S. Salomons,[1] Silvy J. M. van Dooren,[1] Nanda M. Verhoeven,[1] Kim M. Cecil,[2] William S. Ball,[2] Ton J. Degrauw,[3] and Cornelis Jakobs[1]

[1]Department of Clinical Chemistry, Metabolic Unit, VU Medical Center, Amsterdam; and Divisions of [2]Radiology, the Imaging Research Center, and [3]Neurology, Children's Hospital Medical Center, and the University of Cincinnati, Ohio

We report the first X-linked creatine-deficiency syndrome caused by a defective creatine transporter. The male index patient presented with developmental delay and hypotonia. Proton magnetic-resonance spectroscopy of his brain revealed absence of the creatine signal. However, creatine in urine and plasma was increased, and guanidinoacetate levels were normal. In three female relatives of the index patient, mild biochemical abnormalities and learning disabilities were present, to various extents. Fibroblasts from the index patient contained a hemizygous nonsense mutation in the gene *SLC6A8* and were defective in creatine uptake. The three female relatives were heterozygous for this mutation in *SLC6A8*, which has been mapped to Xq28.

Défice do transportador da creatina (SLC6A8)



↓ Creatina cerebral

Défice do transportador da creatina

Heterogeneidade fenotípica

+ comuns: DI, pert linguagem, PHDA, traços autistas

Outras manifestações possíveis: hipotonia, hiperlaxidão, baixa estatura, atrofia cerebral, arritmias…

Fenótipo **mais grave** no género masculino, **mas** possíveis DI ligeiro a moderado e epilepsia variável nas meninas

Hum Genet (2006) 119: 604–610
DOI 10.1007/s00439-006-0162-9

ORIGINAL INVESTIGATION

578 masc DI etiol desc

Amy J. Clark · Efraim H. Rosenberg
Ligia S. Almeida · Tim C. Wood · Cornelis Jakobs
Roger E. Stevenson · Charles E. Schwartz
Gajja S. Salomons

X-linked *creatine transporter* (*SLC6A8*) mutations in about 1% of males with mental retardation of unknown etiology

Variabilidade fenotípica e laboratorial

JMG

Phenotype and genotype in 101 males with X-linked creatine transporter deficiency

J M van de Kamp, O T Betsalel, S Mercimek-Mahmutoglu, et al.

J Med Genet 2013 50: 463-472 originally published online May 3, 2013
doi: 10.1136/jmedgenet-2013-101658

Pediatric Neurology 46 (2012) 39–41

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Case Report

Phenotypic Variability in a Portuguese Family With X-Linked Creatine Transport Deficiency

Paula Garcia MD [a], Fidjy Rodrigues MSc [a], Carla Valongo MSc [b], Gajja S. Salomons MD [c], Luísa Diogo MD, PhD [a,*]

[a] Unidade de Doenças Metabólicas, Centro de Desenvolvimento Luís Borges, Hospital Pediátrico de Coimbra, Coimbra, Portugal
[b] Centro de Genética Médica Jacinto de Magalhães, Instituto Nacional de Saúde Dr. Ricardo Jorge, Porto, Portugal
[c] Metabolic Unit, Department of Clinical Chemistry, Vrije Universiteit University Medical Center Amsterdam, Amsterdam, The Netherlands

ARTICLE INFORMATION

Article history:
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Accepted 5 October 2011

ABSTRACT

Cerebral creatine transporter deficiency, attributable to mutations in the *SLC6A8* gene, causes X-linked mental retardation, language delay, epilepsy, and autistic features. In contrast with creatine synthesis defects, the vast majority of patients with *SLC6A8* deficiency do not respond to treatment. We describe a Portuguese family with a mutation (c.456C>T; p.Gln486X) in the *SL6CA8* gene: two adult monozygotic twin brothers, with psychomotor delay and severe speech impairment. The family also includes their maternal half-sister with psychomotor retardation, predominantly in language, and their mentally retarded mother. This family illustrates the remarkable phenotypic variability in this condition. Investigation of creatine metabolism is mandatory in patients with developmental delay of unknown etiology, to detect this condition.

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2011: 79: 264–272
Printed in Singapore. All rights reserved

CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2010.01460.x

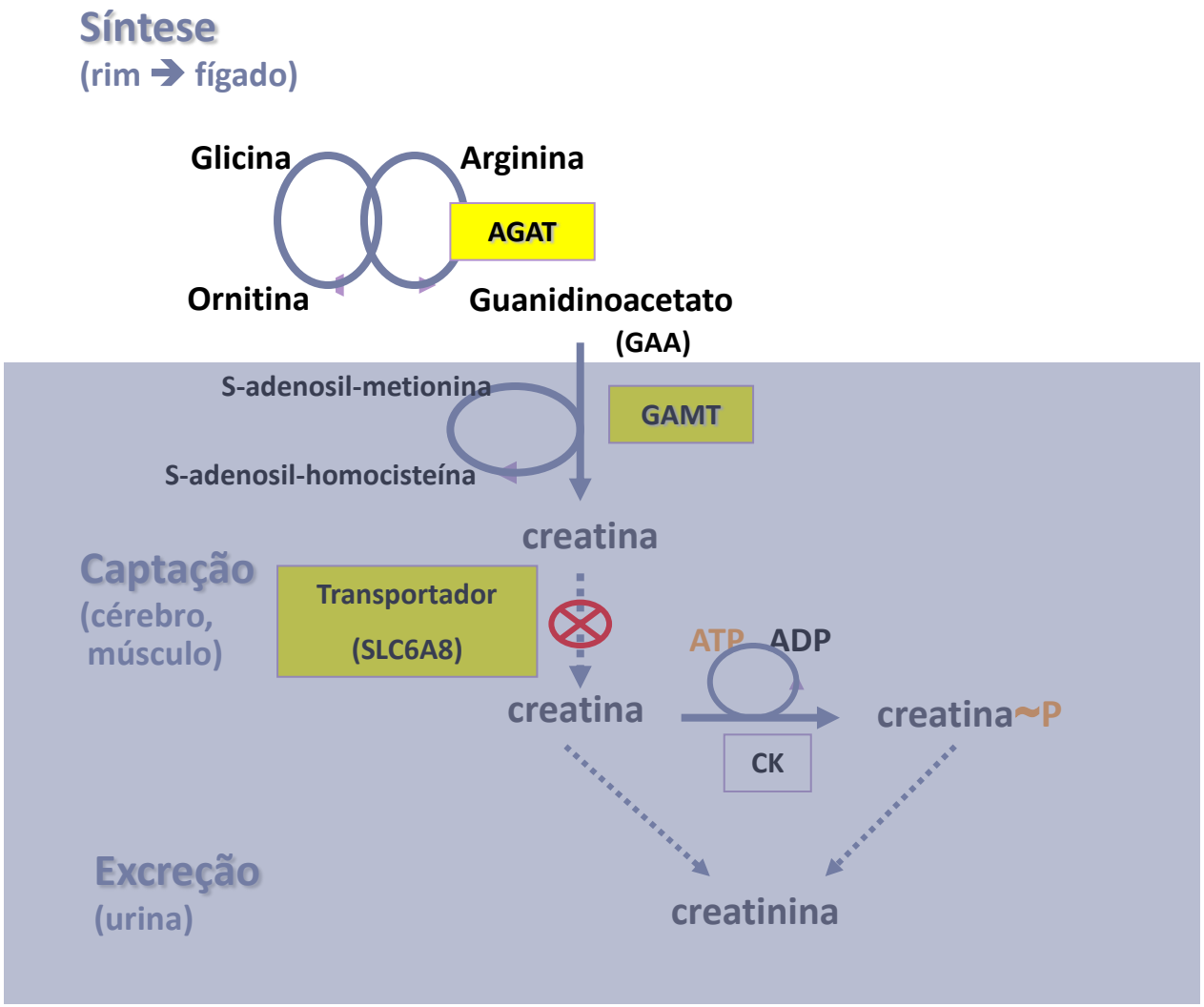
Short Report

Clinical features and X-inactivation in females heterozygous for creatine transporter defect

van de Kamp JM, Mancini GMS, Pouwels PJW, Betsalel OT, van Dooren SJM, de Koning I, Steenweg ME, Jakobs C, van der Knaap MS, Salomons GS. Clinical features and X-inactivation in females heterozygous for creatine transporter defect.
Clin Genet 2011: 79: 264–272. © John Wiley & Sons A/S, 2010

The creatine transporter defect is an X-linked cause of mental retardation. We investigated the clinical features and pattern of X-inactivation in a Dutch cohort of eight female heterozygotes. We show that symptoms of the creatine transporter defect (mental retardation, learning difficulties, and constipation) can be present in female heterozygotes. We further show that the diagnosis in females is not straightforward: (i) The creatine/creatinine ratio in urine was elevated only in three of eight females. (ii) Although as a group the females had a significantly decreased cerebral creatine concentration, individual females had creatine concentrations overlapping with normal controls. (iii) Skewed X-inactivation was found in the cultured fibroblasts, in favour of either the mutated or the wild-type allele, leading to either deficient or normal results in the creatine uptake studies in fibroblasts. Thus, screening by these tests is unreliable for the diagnosis. In addition, we found no consistent skewing of the X-inactivation in peripheral tissues indicating that there is no selection against the creatine transporter defect. We conclude that testing for creatine transporter defect should be considered in females with (mild) mental retardation. Screening by DNA analysis of the *SLC6A8* gene is recommended.

Défice de AGAT



↓ Creatina
↓ GAA

Défice de AGAT

Três famílias descritas (2012)

Genética: gene AGAT; 15q15.3; transmissão AR

Primeira família:

3 irmãos e 1 primo; ADPM/DI, AL, autismo, epilepsia variável; 1 dg neonatal com tto aos 4 meses ⇒DPM N 18M

Outras manifestações descritas: miopatia, CK ↑

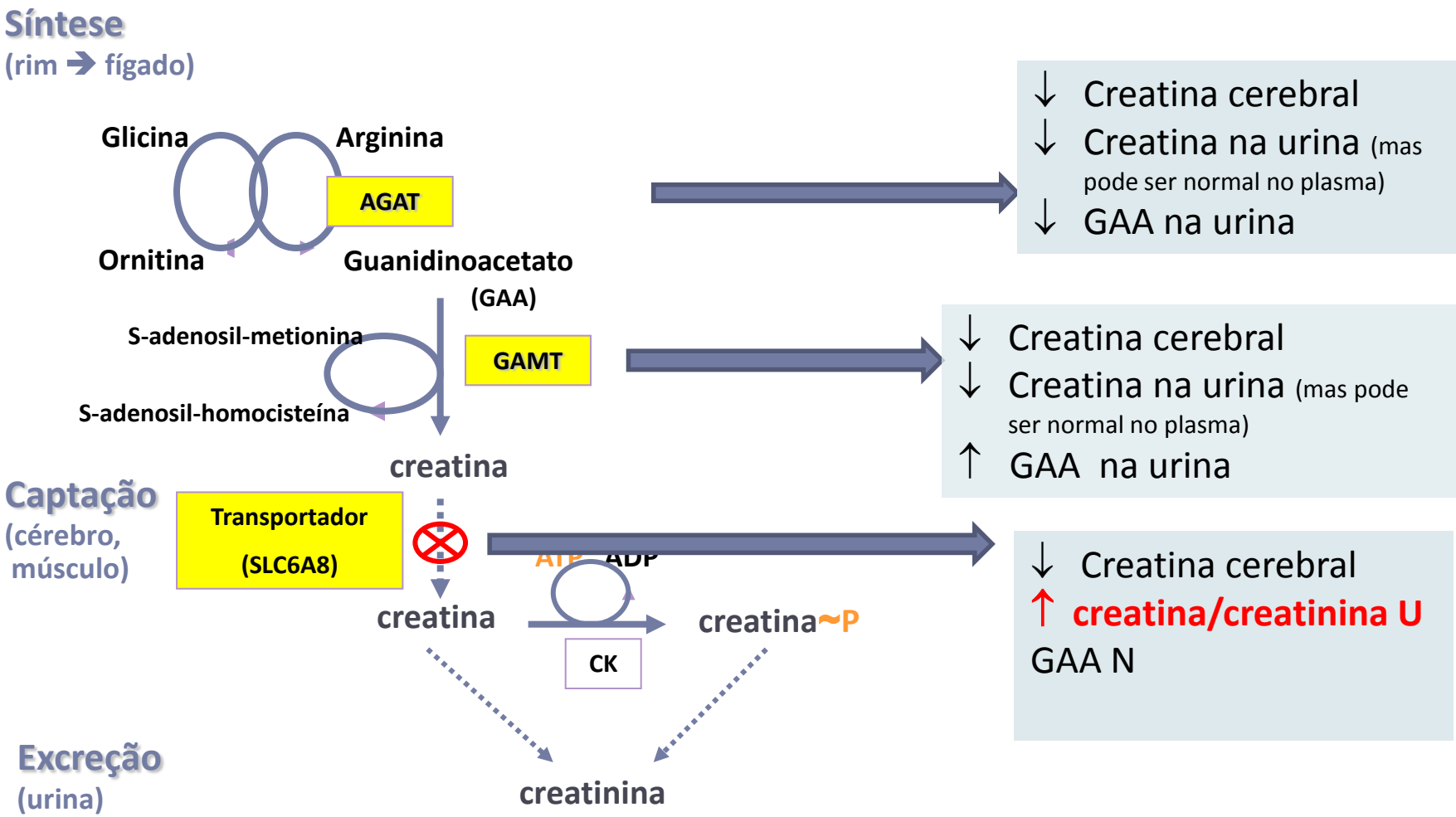
CLINICAL AND LABORATORY OBSERVATIONS

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)*

Alterações bioquímicas



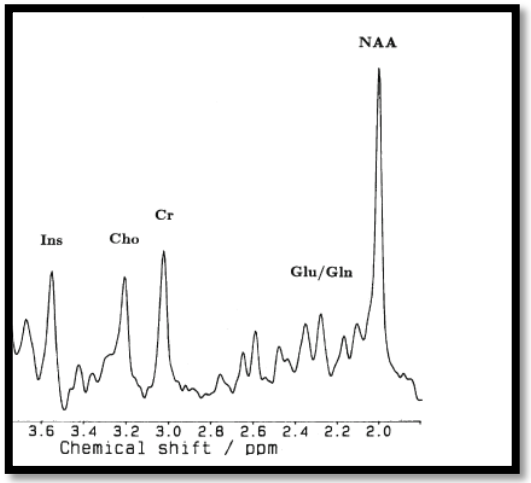
Alterações laboratoriais

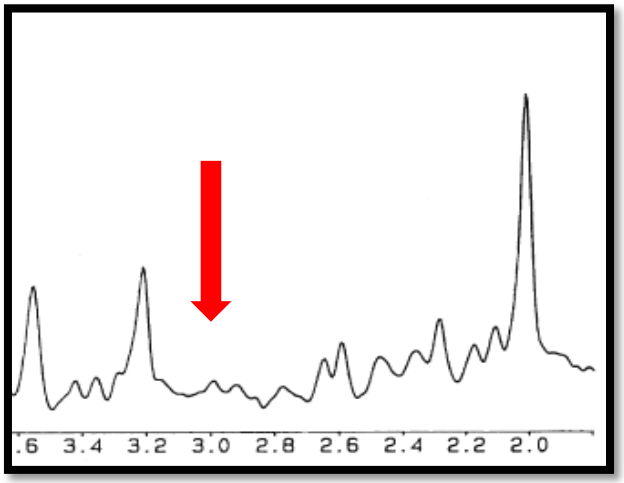
	Défice de AGAT	Défice de GAMT	Défice de SLC6A8 *
Creatina (urina)	↓	↓	**N/↑**
GAA (urina) +	**N/↓**	↑	**N**
Creatina/creatinina (U)	**N**	**N**	↑

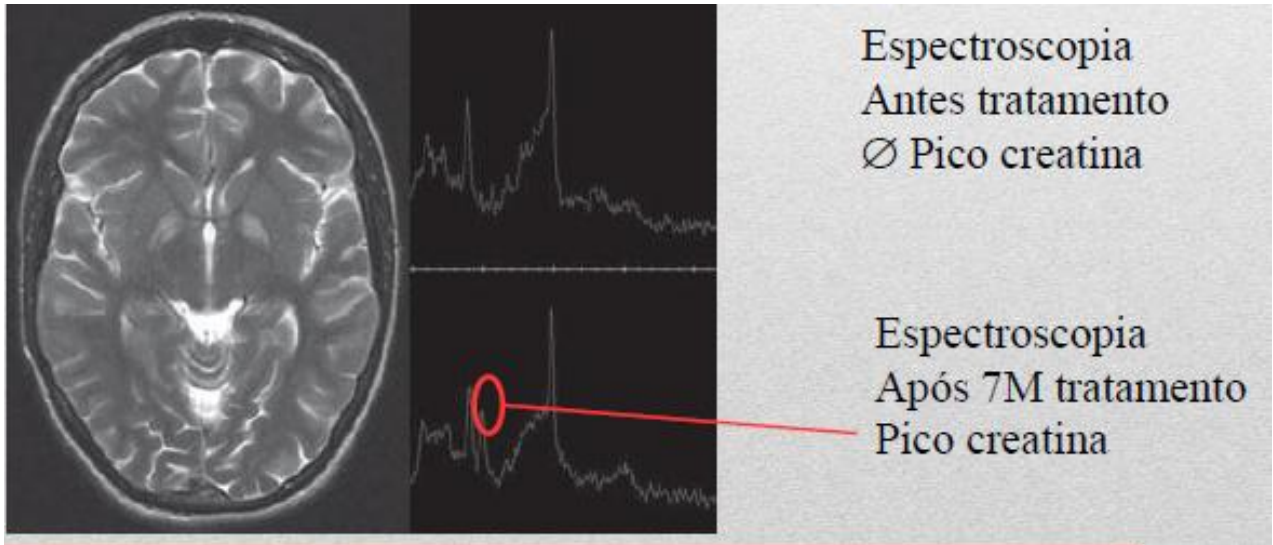
* Nas heterozigotas o ratio creatina/creatinina (U) pode ser normal…

+ GAA pode ser doseado em cartão

RMN-CE com espectroscopia







O'Rouke D, Ryan S, Salomons G, Jakobs C, Monavari A, King M. GAMT deficiency: late onset of movement disorder and preserved expressive language. Developmental medicine & child neurology 2009, 51:404-407

Diagnóstico dos Défices de Creatina Cerebral

Estudos laboratoriais

Creatina(U)

GAA (U)

Creatina/Creatinina (U)

	Défice de AGAT	Défice de GAMT	Défice de SLC6A8 *
Creatina (urina)	↓	↓	N/↑
GAA (urina) +	N/↓	↑	N
Creatina/creatinina (U)	N	N	↑

RMN-CE com espectroscopia (se RMN indicada)

Estudo dos genes GAMT, AGAT, SLC6A8 (confirmação dg; utilidade nas heterozigotas)

Estudos funcionais/enzimáticos (investigação, mutações de patogenicidade desconhecida)

Tratamento dos Défices de Creatina Cerebral

Nos défices de AGAT e GAMT

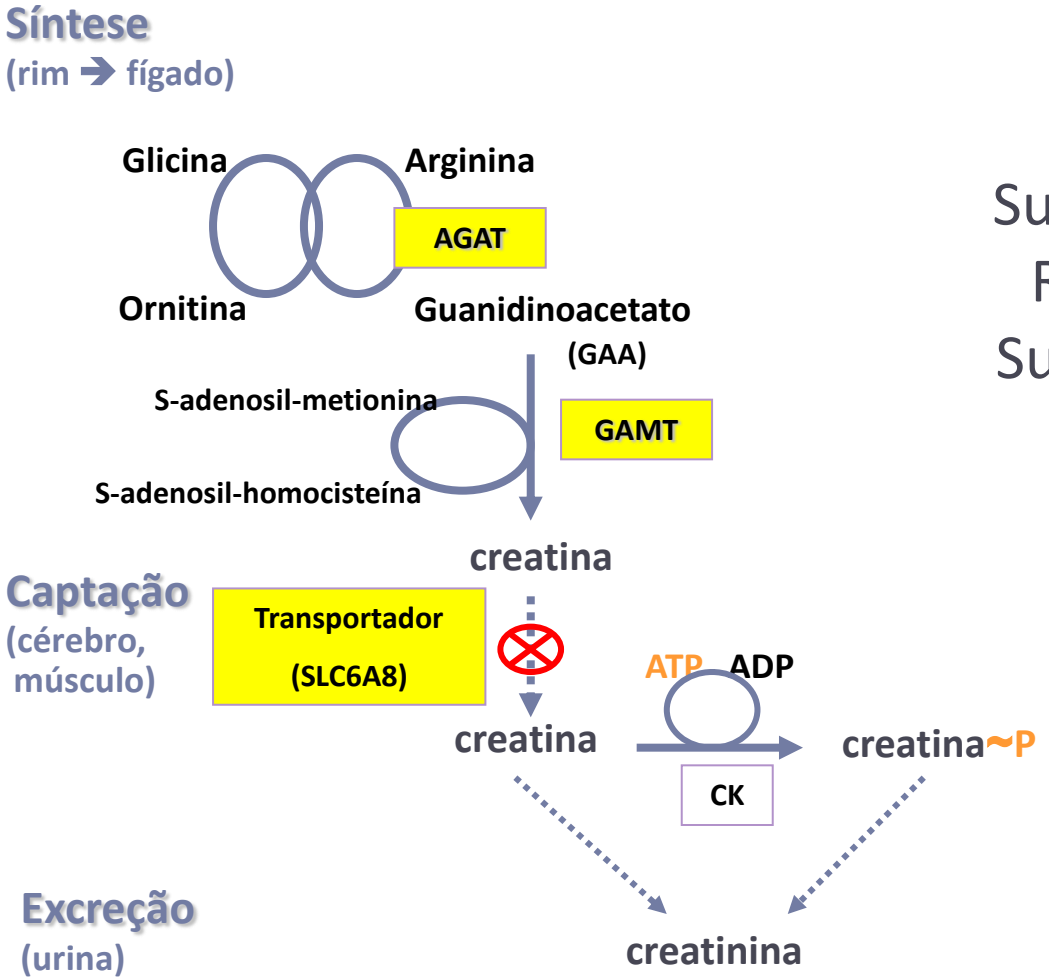
Objetivos:

↑ Creatina cerebral (def de AGAT e de GAMT) → Monohidrato de creatina (300-400 mg/Kg/dia)

↓ GAA (def de **GAMT**)

Restrição de arginina
Suplementação com ornitina

Tratamento de Défice de GAMT



Suplemento de creatina
Restrição de arginina
Suplemento de ornitina

O mais precoce possível

Prognóstico

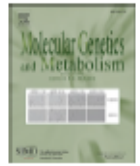
Doenças recentes... teoricamente bom prognóstico se tratamento precoce

Molecular Genetics and Metabolism 105 (2012) 155–158

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Brief Communication

Evaluation of two year treatment outcome and limited impact of arginine restriction in a patient with GAMT deficiency

Saadet Mercimek-Mahmutoglu [a,b,*], Mary Dunbar [c], Andrea Friesen [d], Susan Garret [d], Carol Hartnett [a], Linda Huh [e], Graham Sinclair [f], Sylvia Stockler [a], Stephen Wellington [g], Petra J.W. Pouwels [h], Gajja S. Salomons [b], Cornelis Jakobs [b]

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[d] Department of Physiotherapy and Occupational Therapy, University of British Columbia, Vancouver, BC, Canada
[e] Division of Neurology, Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
[f] Biochemical Genetics Laboratory, Department of Pathology, University of British Columbia, Vancouver, BC, Canada
[g] Division of Developmental Pediatrics, Department of Pediatrics, University of British Columbia, Vancouver, Canada
[h] Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

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Available online 6 October 2011

Keywords:
GAMT deficiency
Autism
Creatine therapy
Global developmental delay

ABSTRACT

A 4-year-old female with history of developmental regression and autistic features was diagnosed with guanidinoacetate methyltransferase deficiency at age 21 months. Upon treatment, she showed improvements in her developmental milestones, sensorial-neural hearing loss and brain atrophy on cranial-MRI. The creatine/choline ratio increased 82% in basal ganglia and 88% in white matter on cranial MR-spectroscopy. The CSF guanidinoacetate decreased 80% after six months of ornithine and creatine supplementation and an additional 8% after 18 months of additional arginine restricted diet. We report the most favorable clinical and biochemical outcome on treatment in our patient.

Available online at www.sciencedirect.com
ScienceDirect
Molecular Genetics and Metabolism 91 (2007) 294–296
Molecular Genetics and Metabolism
www.elsevier.com/locate/ymgme

Brief Communication

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]

[a] Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, The Netherlands
[b] Radiology, University Medical Centre Groningen, University of Groningen, The Netherlands
[c] Division of Clinical and Metabolic Genetics, Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada
[d] Pediatric Neurology, University Medical Centre Groningen, University of Groningen, The Netherlands
[e] Department of Clinical Chemistry, Metabolic Unit, VU University Medical Centre, Amsterdam, The Netherlands

Received 19 March 2007; accepted 19 March 2007
Available online 26 April 2007

Abstract

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.

Discussion

Clinical improvements after the start of treatment at the age of 3 years and 8 months in this GAMTD patient exceeded those observed in most previously treated patients [1].

The question is whether this improvement is caused by aspects of the individual patient or by the treatment strategy.

Ideal: tratamento pré-sintomático ou o mais precoce possível

Diagnóstico precoce
mas variabilidade fenotípica…clínica inespecífica … diagnóstico "fácil"

Inclusão no dg neonatal?
(talvez em Portugal se justifique…)

Síndromes de Deficiência Cerebral de Creatina

Cerebral Creatine Deficiency Syndromes

Rui MALHEIRO, Luísa DIOGO, Paula GARCIA, Isabel FINEZA, Guiomar OLIVEIRA
Acta Med Port 2012 Nov-Dec;25(6):389-398

RESUMO

Introdução: As síndromes de deficiência cerebral de creatina (OMIM 300036) são um grupo de patologias recentemente descritas, caracterizadas por defeitos congénitos no metabolismo da creatina. A apresentação clínica compreende um espectro variado de perturbações do neurodesenvolvimento. Os baixos níveis de creatina cerebral verificados nestes doentes devem-se a diferentes mutações nos genes que codificam as enzimas de síntese da creatina [arginina:glicina amidinotransferase (AGAT, EC 2.1.4.1), e metiltransferase do ácido guanidinoacético (GAMT, EC 2.1.1.2)], AGAT e GAMT, respectivamente, ambas de transmissão autossómica recessiva, ou o seu transportador (CT1), SLC6A8, de transmissão ligada ao cromossoma X.

Objectivo: Caracterizar o espectro de apresentação clínica e laboratorial dos doentes com o diagnóstico da síndrome de deficiência de creatina cerebral seguidos no Hospital Pediátrico Carmona da Mota, bem como a sua orientação diagnóstica e terapêutica. A divulgação destes erros inatos do metabolismo enquanto doenças neurológicas, nomeadamente do neurodesenvolvimento, entre a comunidade médica é outro dos propósitos almejados.

Material e Métodos: Análise retrospectiva dos processos clínicos de doentes com o diagnóstico de deficiência cerebral da creatina seguidos no Hospital Pediátrico.

Resultados: Foram identificados doze doentes com défice cerebral da creatina pertencentes a sete famílias. Cinco apresentam deficiência de metiltransferase do ácido guanidinoacético e sete do transportador de creatina. Têm actualmente entre dois e 38 anos. Os principais motivos de consulta foram: atraso global de desenvolvimento em sete doentes, dois dos quais também apresentavam epilepsia, e atraso da linguagem em outros dois. Apenas num caso o motivo de consulta foi défice de interacção social e de comunicação. Em todos os casos se registou um quociente de desenvolvimento global na faixa da deficiência intelectual. O estudo imagiológico demonstrou o padrão patognomónico destas síndromes em oito doentes. No estudo genético foram identificadas mutações nos genes GAMT ou SLC6A8 nos doze casos.

Conclusões: A suspeita de deficiência de creatina cerebral deve ser considerada em todos os casos de atraso de desenvolvimento psicomotor sem outra causa evidente. A terapêutica pré-sintomática tem mostrado resultados promissores em algumas crianças com défice cerebral de creatina, sobretudo nos défices de GAMT. A elevada taxa de portadores de mutações do gene GAMT em Portugal torna esta anomalia elegível para o rastreio neonatal no nosso País.

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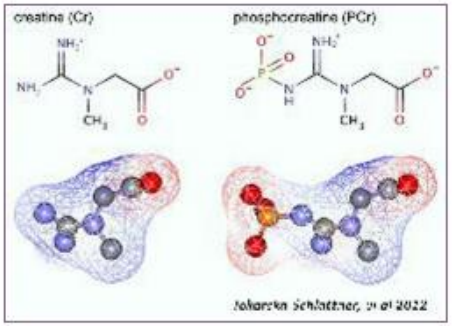
Doenças Hereditárias
do Metabolismo

XI Curso Básico



23 a 25 setembro 2013

CASA DA ACREDITAR

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Obrigada!

Carolina Duarte