



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

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Cerebral creatine deficiency syndromes (CCDSs) are inborn errors of metabolism that include two autosomal recessive creatine biosynthesis defects (arginine-glycine amidinotransferase [AGAT; OMIM 602360] and guanidinoacetate methyl transferase [GAMT; OMIM 601240] deficiency) and an X-linked creatine transporter defect (OMIM 300036).¹ The clinical phenotype is variable, associating nonspecific mental retardation, epilepsy, extrapyramidal movement disorders, and autistic behavior. The frequency of CCDS is unknown and probably underestimated. We report a high frequency of CCDS in mentally retarded children, mostly boys with an X-linked creatine transporter deficiency.

Methods. Over a period of 18 months, children referred to the Department of Pediatric Neurology with unexplained mild to severe mental retardation, normal karyotype, and absence of fragile X syndrome were prospectively screened for CCDS. Children were from diverse ethnic backgrounds. Children with polymalformative syndromes were excluded. Creatinine metabolism was evaluated using creatine/creatinine and guanidinoacetate (GAA)/creatinine ratios on a spot urine.² Diagnosis was further confirmed using brain proton MR spectroscopy (H-MRS) and mutation screening by DNA sequence analysis in either the *SLC6A8* (creatine transporter defect) or the *GAMT* genes.

Results. One hundred eighty-eight children were eligible to participate: 114 boys (61%) and 74 girls (39%); 118 children (63%) were severely retarded and 70 (37%) had mild to moderate mental retardation. Family history revealed 151 (80%) sporadic cases and 37 (20%) familial cases (siblings or first-degree relatives). Four boys from four unrelated families had elevated creatine/creatinine ratio, suggesting a creatine transporter defect. In another boy, elevated urinary GAA/creatinine ratio suggested GAMT deficiency. H-MRS and molecular investigation confirmed the diagnosis, and five new mutations either in the *SLC6A8* or *GAMT* gene were identified. All five patients presented with severe mental retardation. Brain MRI showed minor and nonspecific abnormalities. Extensive clinical, radiologic, and biologic characteristics are depicted in the table on page 1714.

The prevalence of CCDS was 2.7% (5/188, CI: 0.36 to 4.96) in the whole population and 4.4% (5/114, CI: 0.63 to 8.15) in boys. None of the 74 girls had a CCDS. In the 151 sporadic cases, prevalence of CCDS was 1.9% (3/151, CI: 0 to 4.21). In the 37 familial cases, the prevalence was 5.4% (2/37, CI: 0 to 12.7).

Discussion. These results show a high prevalence of CCDS either in sporadic or in familial unexplained mental retardation, especially in boys. The five diagnoses were suspected on the basis of increased urine creatine/creatinine or GAA/creatinine ratios measured as described elsewhere.² H-MRS revealed the lack of creatine peak in all patients except for Case 2, for whom the parents refused the analysis. All mutations were highly likely to be pathogenic due to either their nature (frame shift or splice error mutations) or location in a very conserved region of the gene. Moreover, we did not identify these mutations in 276 control chromosomes, and familial segregation was confirmed for each mutation. In our study, all boys presented late-onset walking and severe to profound mental retardation; three boys had autistic features, consistent with the existing literature.³ Brain MRI

showed a thin corpus callosum³ in three patients with transporter defect. As expected, we did not observe any creatine transporter defect in mentally retarded girls.⁴ However, GAMT and AGAT deficiencies, which are sensitive to creatine intake, may affect girls and should be measured in both boys and girls with mental retardation.

High prevalence of mutations in the *SLC6A8* gene (2.1%) was reported in a panel of 288 boys with nonspecific mental retardation.⁵ However, this population was composed only of familial cases. Recently, another study evoked the presence of a *SLC6A8* mutation in approximately 1% of boys with mental retardation of unknown etiology.⁶ Another study reported a high prevalence (2.7%) of GAMT deficiency in 180 adults and children with severe mental handicap in an isolated population.⁷

We report a prospective biochemical screening method for CCDS in mentally retarded boys and girls, with sporadic or familial cases, from different ethnic backgrounds recruited in one Department of Pediatric Neurology. The high prevalence of CCDS in our study population (2.7%) suggests that urinary screening of creatine/creatinine and GAA/creatinine ratio should be considered in all patients with mental retardation.

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Table Clinical and biochemical presentation of the five patients affected with creatine deficiency syndrome

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Disease	Creatine transporter defect	Creatine transporter defect	Creatine transporter defect	Creatine transporter defect	GAMT deficiency
Family history					
Sporadic/familial	Familial	Sporadic	Sporadic	Familial	Sporadic
Consanguinity	No	No	No	No	Yes
Ethnic origin	White	Gipsy	White	White	North African
Clinical data					
Current age, years	4	6	8	14	10
Age at walking, months	22	14	19	24	30
Neurologic examination	Normal	Stilling-Duane Sd	Brisk reflex	Normal	No obvious dystonia
Epilepsy	No	No	No	Yes (GTCS)	Yes (GTCS)
Head circumference	Median	-1 SD	-2.5 SD	-2 SD	+1 SD
Neuropsychological profile					
Mental age (Vineland)*	20 mo.	2 y 5 mo.	4 y 11 mo.	30 mo.	25 mo.
Cognitive level IQ/DQ**	DQ = 38	IQ < 40	IQ < 40	IQ < 20	DQ < 20
Expressive language	3 words	20 words	10 words	50 words	30 words
Autistic behavior	Yes	No	No	Yes	Yes
Brain imaging					
MRI morphology	Hypersignal in posterior white matter	Thin corpus callosum	Thin corpus callosum	Left caudate and hippocampus atrophy	Normal
H-MRS	No creatine peak	Not performed	No creatine peak	No creatine peak	Low creatine peak
Biological data (urine)					
Creatine/creatinine ratio (age-matched control range)	2.3	2.5	2.7 (0.02 - 0.7)	2.1	0.08
GAA (mmol/mol creatinine) (age-matched control range)	75.1	116.9	85.2 (4-220)	48.4	300
Molecular data	SLC6A8 c.395G>T p.Gly132Val	SLC6A8 c.1417_1420del TTTG p.Phe473Thr fsX37	SLC6A8 c.912G>A skipping of exon 5 (r.772_912del)	SLC6A8 c.1473C>G p.Cys491Trp	GAMT c.148A>C p.Met50Leu

* Vineland Adaptive Development Scale.

† Standardized psychometric tests (Wechsler Intelligence Scale for Children III, Brunet-Lézine).

IQ = total IQ; DIQ = developmental IQ; MRS = MR spectroscopy; GAA = guanidinoacetate.

Thyroid replacement therapy and atrial fibrillation in acute ischemic stroke

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Atrial fibrillation is a risk factor for ischemic stroke.¹ Hyperthyroidism is a cause of atrial fibrillation. Subclinical hyperthyroidism, also associated with atrial fibrillation, may result from excess thyroid replacement therapy.^{2,3} However, it is unclear whether thyroid replacement therapy is a risk factor for atrial fibrillation in patients with acute ischemic stroke. In this case-control study, we sought to determine the association between thyroid replacement therapy and atrial fibrillation in patients presenting with ischemic stroke.

Methods. The study protocol was approved by the local Institutional Research Board at Stanford University Medical Center. We identified consecutive patients with ischemic stroke with atrial fibrillation (cases) and without atrial fibrillation (controls) admitted to the Stanford Stroke Center between 1996 and 2004 through a local stroke registry database. The stroke registry (3,276 sub-

jects) includes patients presenting with ischemic stroke, TIA, hemorrhagic stroke, and patients in whom stroke was suspected but excluded. Cases and controls were frequency matched for age (within 5 years) and gender. To improve our power to detect associations, we sought to select two controls for each case. The following data were abstracted from the electronic admission records by one investigator, using a standardized case report form: age, gender, known atrial fibrillation or atrial fibrillation diagnosed during hospital admission, stroke subtype (attending clinician using TOAST criteria), thyroid replacement therapy use on admission, diabetes mellitus, hypercholesterolemia, smoking, hypertension, coronary heart disease, amiodarone use, and preadmission anti-thrombotic therapy.

Statistical analysis. Odds ratios (ORs) with 95% CI were calculated by logistic regression analysis. In evaluating two-way interaction terms, we postulated an interaction between amiodarone therapy and thyroid replacement therapy.³ Individual variables previously shown to affect the risk of atrial fibrillation were included in the multivariable binary logistic regression model. The Hosmer-Lemeshow test for goodness of fit was performed.⁴ Analyses were performed using Minitab 14 (State College, PA).