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

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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)***

Three primary disorders of creatine (Cr) metabolism causing brain Cr depletion have been described, involving defects of guanidinoacetate-methyltransferase (GAMT; E.C. 2.1.1.2), arginine:glycine amidinotransferase (AGAT; E.C. 2.1.4.1), or brain Cr transporter (CRTR).[1-3] Brain Cr content can be corrected with oral supplementation of Cr in the first 2 disorders. AGAT deficiency (OMIM 602360), an autosomal recessive disease, is characterized by mental retardation, severe language impairment, and behavioral disorders. Oral Cr supplementation was shown to improve clinical symptoms in previously reported cases.[4,5] Because no patient has been diagnosed in the presymtomatic phase of the disease, the efficacy of early treatment in preventing the phenotypic expression of AGAT disorder remains to be proven.

We report the results of early Cr supplementation in the first newborn affected by AGAT deficiency that was diagnosed while the patient still had no symptoms.

CASE REPORT

The patient was the 18-month-old son of healthy non-consanguineous Italian parents carrying the W149X mutation in the AGAT gene.[5] Two older daughters were affected by AGAT deficiency.[6] Although informed about the risk of recurrence of the disease, the parents refused consent for prenatal diagnosis. The infant was born after an unremarkable pregnancy, labor, and delivery (birth weight: 3 kg; length: 49 cm; head circumference: 35 cm). The results of a neurological examination, performed when the patient was 3 days old, were normal. However, plasma and urine levels of guanidinoacetic acid (GAA) and Cr were low and further decreased at 15 days (Table). Sequencing of the AGAT gene demonstrated the same homozygous W149X mutation that affected the siblings,[7] and AGAT activity in the lymphoblasts was undetectable.

When the patient was 3 weeks old, an almost complete absence of cerebral total Cr peak at 3.05 ppm was shown by means of brain proton magnetic resonance spectroscopy (^{1}H-MRS; Figure, A), confirming the diagnosis of AGAT deficiency.

To correct the Cr depletion, because the infant was breastfed, we initially tried to supplement the mother's diet with Cr monohydrate (3-9 g/day). This therapeutic approach was attempted because of the lack of knowledge about the toxicity of direct Cr supplementation to infants. Moreover, breastfeeding could have a protective role, explaining the delay in the onset of neurological symptoms in previously described cases, in which the patients were also breastfed. Although mother's supplementation resulted in an increase of Cr concentration in maternal milk (190 μM; n.v. 82.29-128.93), an increase in the Cr concentration in the infant's blood, urine, and brain was not demonstrated (Table).

^{1}H-MRS	Proton magnetic resonance spectroscopy	Cr	Creatine
AGAT	Arginine:glycine amidinotransferase	GAA	Guanidinoacetic acid

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Table. Biochemical findings with different creatine supplementation

Age	Therapy	Plasma		Urine		Lymphoblasts	Maternal milk
		Cr *μmol/L*	GAA *μmol/L*	Cr *μmol/L*	GAA *μmol/L*	AGAT activity *nmol/mg pr/h*	Cr *μmol/L*
At birth	none	16.2	0.13	24.6	0.54		
15 days	none	3.2	0.04	20.7	0.34	n.d.	90.18
2 months	After 1 month of supplementation of mother (3 g/day)	4.04	n.d.	6.3	n.d.		179.03
4 months	After 3 months of supplementation of mother (9 g/day)	55.1	n.d.	76.0	n.d.	-	185.4
5 months	After 1 month of supplementation of infant (100 mg/Kg/day)	221.7	n.d.	1754.0	n.d.	-	-
7 months	After 3 months	164.2	n.d.	4324.1	n.d.	-	-
10 months	After 6 months	172	n.d.	53513	n.d.	-	-
13 months	After 9 months	222	n.d.	15058.9	n.d.	-	-
17 months	After 13 months	156.5	n.d.	16378.3	n.d.	-	-
Control subjects		18–141	0.22–3.14	200–5500	55–698	0.95–1.47	82.29–128.93

Plasma and urine levels of Cr and GAA and AGAT activity were measured by GC/MS as reported by Alessandri et al.[7] The Cr levels in mother's milk were comparable with that in the literature.[10]
n.d., Not detectable.

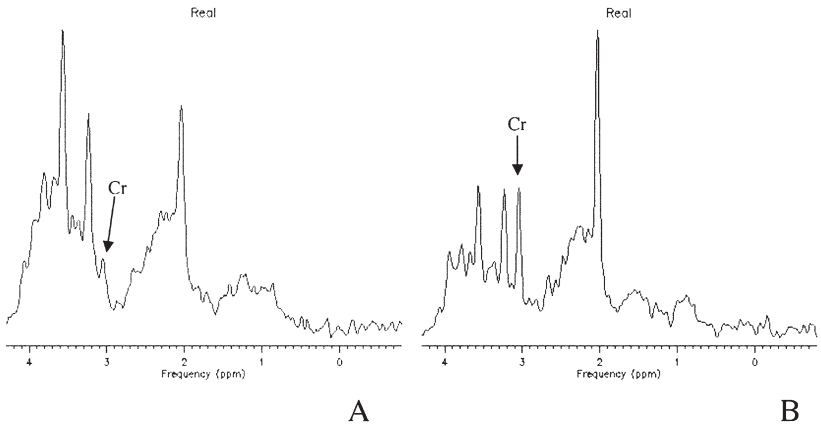

Figure. [1] H-MRS of the patient at birth (A) and at 12 months, after 8 months of Cr oral supplementation (B). Note the absence of Cr peak at 3.05 ppm at birth and its partial restoration after early treatment. Other differences in the spectrum are caused by physiological changes for age: Myoinositol (mI) is higher and N-Acetilaspartate (NAA) is lower at birth than at 12 months.

When the patient was 4 months old, after weaning, diet supplementation of the infant with Cr monohydrate was initiated. Because of the lack of toxicological data for infants, we started with a low dosage of oral Cr (100 mg/bw/day) divided in 5 doses. With a subsequent assessment of plasma and urine Cr levels, a progressive replenishment of body Cr pools by the end of the first week of treatment was revealed (Table). Plasma concentration of Cr overlapped those obtained in the affected relatives with higher dosages.[4,5] At 12 months of age and after 8 months of treatment, a restoration of about 60% of normal brain Cr was demonstrated by means of a brain [1] H-MRS examination (Figure, B).

The somatic and psychomotor development of the infant remained totally normal. At the age of 12 months, he walked unaided and uttered single words. At 16 months, he was able to ask by means of sign indication, and from the age

of 18 he produced some two-word combinations and understood simple verbal requests. His general developmental quotient was 105 by using the Griffiths Developmental Scales.

Early Cr supplementation was well tolerated, and the only adverse effect was transient episodes of diarrhea when the treatment started or when the dose was increased for weight gain.

DISCUSSION

AGAT deficiency is the least common form of the 3 known inborn errors of Cr metabolism. GAA and Cr reductions in biological fluids are its biochemical markers,[8] and mental retardation with autistic behavior are the clinical hallmarks of this disorder.[4,5] We report an inborn error of Cr metabolism diagnosed during the neonatal period and treated while the infant still had no symptoms.

We showed that blood GAA and Cr are both low from the first days of life, supporting their use as early diagnostic markers for AGAT deficiency.[8] They can be analyzed in plasma, as reported here, and in dry blood spots,[9] in which GAA concentrations are a highly sensitive diagnostic marker. We also found that a severe brain Cr depletion, as detected by using ^{1}H-MRS, was already present at 2 weeks of life. In healthy adults, approximately 2% of total Cr pool is lost every day as creatinine and needs to be replaced from exogenous supplies or by endogenous synthesis.[1] Therefore, the low early values of brain Cr suggest a prenatal brain Cr depletion or, alternatively, a more rapid turnover of Cr in the brain during the first weeks of life. The delay in the onset of neurological symptoms, a feature shared by all the disorders of Cr metabolism and transport,[2,3] cannot be related to the presence of Cr supplied by the mother during fetal life. Moreover, even if Cr is a component of maternal milk, we found that breastfeeding did not maintain Cr pools in this infant. As an alternative hypothesis, we suggest that the latency in clinical manifestation of Cr disorders may be related to a relatively low need of the Cr/phosphocreatine system during the early phases of brain development.

This case supports the view that AGAT deficiency is a curable metabolic disorder. At the age of 18 months, the patient had normal growth parameters and developmental quotients, whereas his affected relatives, at the same age, already showed a severe delay in somatic growth and psychomotor development, associated with hypotonia and autistic-like behavior.[4,5] Moreover, although a significant depletion of brain Cr was detected in our patient, the 4-month delay in treatment appears not to have affected his psychomotor development so far. The Cr dosage we used was about one fourth of that used in previously reported cases of patients who were AGAT deficient[4,5] and proved to be safe and effective in replenishing peripheral Cr pool and (partially) brain Cr pool.

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