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Secondary creatine deficiency in ornithine delta-aminotransferase deficiency

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ABSTRACT

Aims: Ornithine delta-aminotransferase (OAT) deficiency causes gyrate atrophy (GA) of the retina, as a consequence of high plasma ornithine concentrations. Because creatine synthesis requires the conversion of arginine and glycine into ornithine and guanidinoacetate, high ornithine concentration inhibits this reaction thus causing secondary creatine deficiency. The aim of this study was to evaluate the neuropsychological features and creatine metabolism in patients with GA.
Methods: The study involved 7 GA patients, aged from 11 to 27 years who underwent neuropsychological evaluation and cerebral proton magnetic resonance spectroscopy (MRS).
Results: Neurocognitive impairment was found in 5/7 patients, including mental retardation (3/7), school failure (1/7), major visuospatial dyspraxia (1/7), aggressive behavior (3/7) and epilepsy (2/7). Two patients had normal neuropsychological evaluation. Cerebral proton magnetic resonance spectroscopy revealed a profound creatine deficiency in all patients. MRS data were confirmed by decreased levels of creatine and/or guanidinoacetate in plasma and urine in all patients.
Conclusions: In our group of patients with GA, we found a high prevalence of neurological impairment, not reported so far, and possibly related to secondary creatine deficiency and hyperornithinemia. We propose to treat mentally retarded GA patients with high doses of creatine, as it may normalize brain creatine levels and help to reduce ornithine levels.

Ornithine delta-aminotransferase (OAT) deficiency is an autosomal recessive condition causing gyrate atrophy (GA) of the retina responsible for blindness beginning during the first decade, as a consequence of high plasma ornithine concentrations [1]. Creatine synthesis requires the reversible conversion of arginine and glycine into ornithine and guanidinoacetate, catalyzed by arginine–glycine amidinotransferase (AGAT; EC 2.1.4.1.), a rate-limiting enzyme in creatine production, effectively inhibited by ornithine in animal models and in humans (Fig. 1). Thus, high ornithine concentrations inhibit this reaction causing secondary creatine deficiency [2,3].

Abnormal concentrations of creatine, an important intracellular energy source for cells, have been demonstrated by 31P-magnetic resonance spectroscopy (MRS) in skeletal muscle of OAT-deficient patients [4,5] who demonstrated selective atrophy and tubular aggregates of type II skeletal muscle fibers at muscle biopsy. Interestingly, these skeletal muscle abnormalities were reversible after creatine administration [6–8].

Patients with GA generally have normal intelligence, as described by Nanto-Salonen et al. [9] However, non-specific EEG abnormalities and premature degenerative changes at brain MRI have been noted as subclinical signs of involvement of the nervous system [10–13]. Finally, a few patients have been described with mental retardation [14–16]. This may possibly be related to creatine deficiency in the brain as a decreased creatine peak at cerebral MRS has been noted in some patients [9].

Here we report our findings in seven patients with GA, five of them with cognitive impairment. The aim of the study was to evaluate cerebral creatine metabolism in these patients using cerebral ^{1}H magnetic resonance spectroscopy [MRS] and to investigate a possible correlation between the severity of the mental retardation, the creatine deficiency and the levels of plasma ornithine.

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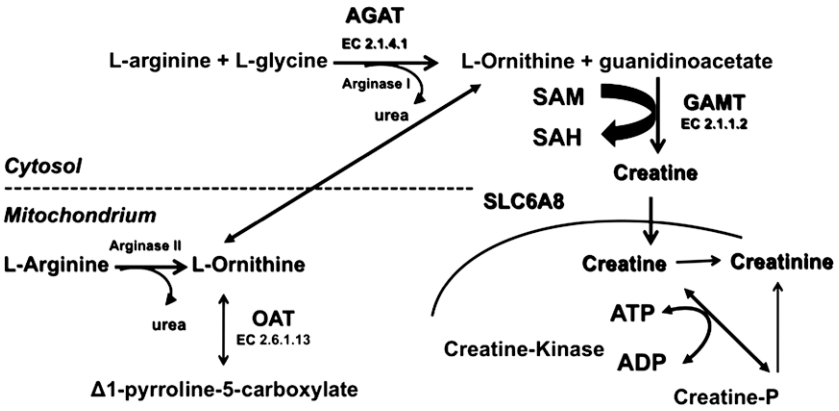

Fig. 1. Creatine metabolism. Ornithine coming from arginine is the immediate precursor of creatine synthesis. High ornithine concentration inhibits arginine–glycine amidinotransferase (AGAT) resulting to deficient creatine synthesis.

Table 1
Clinical characteristics of seven patients with OAT deficiency. The age and the clinical presentation of the GA diagnosis in the 7 patients, the age at time of cerebral MRS, biological parameters (urine and/or plasma ornithine, creatine, guanidinoacetate levels), MRS cerebral metabolite concentrations and metabolite ratios, and the intellectual capacity and behavioral problems for each patient are shown Abnormal values are shown in bold characters.

Patients, sex	Patient 1, M	Patient 2, F	Patient 3, M	Patient 4, M	Patient 5, F	Patient 6, M	Patient 7, M
Age of diagnosis (years)	10	9	9	10	10	10	12
Neuropsychological symptoms at diagnosis:	Educational difficulties	Specialized education, psychological problems	Headaches	Psychomotor retardation, epilepsy	UN	Educational difficulties	Hyperactivity-attention-deficit disorder
Ornithine levels at diagnosis (μmol/l, $N < 100$)	940	945	441	1600	721	859	1032
Age at time of study (years)	11	17	13	27	21	18	24
Neurological evaluation at time of study (visual handicap taken into account)	Major visuospatial dyspraxia verbal IQ:96 perform IQ:57	Severe mental retardation: IQ 54	Normal education IQ: 92 (N)	Severe mental retardation: IQ 59 Epilepsy	School failure, IQ 74	Mental retardation: IQ 70 Epilepsy	Normal education: IQ 97
Psychological evaluation at time of study	Normal behavior	Behavior problems with family Low self-esteem, self-destructive behavior	Normal behavior	Normal behavior	Behavior problems with family Low self-esteem	Aggressive behavior	Hyperactivity-attention deficit disorder Imprisoned
Ornithine level at time of study (μmol/l)	1197	1036	399	969	800	ND	838
Creatine in							
Plasma ($15 < N < 98$ μmol/l)	ND	**4.9**	**6.7**	**6**	**4.8**	ND	**7.3**
Urine ($17 < N < 720$ μmol/mmol creatinine) at time of study	20 and 26	48	50	49	**14**	ND	48
Guanidinoacetate in							
Plasma ($1 < N < 3.5$ μM) at time of study	ND	**0.47**	**0.4**	**0.3**	**0.6**	ND	**0.61**
Urine (μmol/mmol creat, $4 < N < 220$) at time of study	**2.5** and **0.6**	**4**	**4**	**2**	**4**	ND	**3**
Cerebral MRI	N	N	N	N	N	N	Punctate WM ABN
NRS creatine level	↓↓↓	↓↓	↓↓↓	↓↓	↓	↓↓	↓↓↓

N, normal; ND, not done; CR: creatine; WM ABN, white matter abnormalities; ↓↓↓, severe decrease in creatine; ↓↓, moderate decrease in creatine; ↓, mild decrease in creatine.

Patients and methods

This retrospective study included 7 patients with GA, aged from 11 to 27 years. The median age at diagnosis was 10 years (9–12 years) (Table 1). Diagnostic criteria for GA were decreased visual acuity due to gyrate chorioretinal atrophy and high plasma ornithine levels (normal range <100 μmol/l) (Table 1).

Neuropsychological development was assessed taking the following parameters into account (1) intellectual performance (developmental quotient or intelligence quotient (IQ) adapted to the visual impaired (normal range: 85–115 (100 ± 15); mental retardation is defined as $IQ \leqslant 70$); (2) academic achievements; (3) behavioral disorders (aggressiveness, attention-deficit disorder, other symptoms). Patients were classified as normal when they had an $IQ > 85$ with normal academic achievement for age and no behavioral disorders, while they were classified as abnormal when they had mental retardation (estimated $IQ \leqslant 70$) requiring "special" education, school failure, and/or displayed a severe behavioral disorder. Cognitive impairment was also considered when severe visuospatial dyspraxia was noted.

Brain MRS was performed using commercially available Probe-P (PRESS) magnetic resonance spectroscopy (General Electric, Mil-