

## 24.1 Introduction

### ■ Creatine Metabolism

The creatine/creatine-phosphate system plays an important role in the storage and transmission of phosphate-bound energy. In humans, creatine is synthesised in liver and pancreas involving arginine and glycine as substrates and arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT) as enzymes (Fig. 24.1) [1]. Creatine accumulates mainly in muscle and brain via an active transmembrane creatine transport system [2, 3] and is utilised in the cellular pool of creatine/creatine-phosphate which, together with creatine kinase and ATP/ADP, provides a high energy phosphate buffering system [4]. Intracellular creatine and creatine-phosphate are non-enzymatically cycled to creatinine, with a constant daily turnover of 1.5% of body creatine. Creatinine is mainly excreted in urine and its daily excretion is directly proportional to total body creatine [5].

### ■ GAMT Deficiency

#### ● *Clinical Presentation*

GAMT deficiency is the first inborn error of creatine metabolism known in humans [6]. This autosomal recessive disorder of creatine synthesis was first described in 1994 [7] in a male patient who was considered to be normal until 4 months of age, when he was noted to have developmental arrest. He gradually developed severe extrapyramidal movements, hypotonia, frequent vomiting and difficulties in handling secretions. His electroencephalogram (EEG) showed very slow background activity and multifocal spike slow waves. Magnetic resonance imaging (MRI) revealed bilateral abnormalities of the basal ganglia (globus pallidus) with signal hypointensities in T1-weighted images and signal hyperintensities in T2-weighted images. The number of new patients is still small, but their different clinical presentation gives rise to the assumption that GAMT deficiency may manifest in a severe or in a moderate clinical phenotype. Patients belonging to the severe phenotype exhibited in-

tractable epilepsy and early global developmental delay. Extrapyrarnidal movement disorders and abnormal signal intensities of the basal ganglia were predominant symptoms in a Kurdish, Welsh and Italian child [8–10]. A moderate phenotype was present in three patients of Dutch and Turkish origin with mental retardation, autistic behaviour, and speech delay [11, 12]. Recently two adult siblings have been described with GAMT deficiency and intractable epilepsy as leading symptoms [13]. Presently about 15 patients with GAMT deficiency have been recognised.

Common denominators of GAMT deficiency such as epilepsy, slow background activity in EEG, global developmental delay, failure of active speech, and altered signal intensities in the basal ganglia are suggestive of major involvement of the grey cerebral matter. As the clinical phenotype varies widely (from predominance of extrapyramidal encephalopathy and intractable epilepsy to moderate mental retardation only), a specific clinical recognition pattern of the disorder has not been worked out so far. Interestingly, patients with GAMT deficiency do not have signs of cardiac myopathy nor do they have pronounced signs of skeletal myopathy, although muscle tissue might be another site of creatine depletion.

#### ● *Metabolic Derangement*

Patients with GAMT deficiency have systemic depletion of creatine and creatine-phosphate due to impairment of de novo creatine biosynthesis. In vivo proton magnetic resonance spectroscopy has shown that patients with GAMT deficiency have extremely low brain creatine concentrations while guanidinoacetate, the immediate precursor of creatine and substrate to the deficient enzyme activity accumulates in unusually high concentrations. In vivo phosphorus magnetic resonance spectroscopy of the brain has further shown that reduced availability of creatine to the action of creatine kinase leads to deficiency of creatine-phosphate [7, 13]. Abundant guanidinoacetate in the brain is phosphorylated instead by creatine kinase and represents the major proportion of high-energy phosphate. In one patient creatine concentration was measured biochemically in a muscle biopsy and was found to be low [7]. In another patient creatine was measured by proton magnetic resonance spectroscopy in the gastrocnemius muscle and was found to be normal [12]. As a consequence of systemic depletion of creatine and creatine-phosphate, the daily rate of urinary creatinine excretion rate is low, as are creatinine concentrations in plasma and CSF [8, 9, 14].

## ■ Other Disorders of Creatine Metabolism

### ● *General Remarks*

GAMT deficiency is the first inborn error of creatine synthesis. On the occasion of the first description of GAMT deficiency, both AGAT and CRTR deficiency have been predicted as an additional possible cause of cerebral brain deficiency [15]. In general, low urinary creatinine excretion may be the first diagnostic hint with regard to both disorders, but in contrast to GAMT deficiency, guanidinoacetate will not accumulate in arginine:glycine amidinotransferase deficiency, and urinary and plasma creatine concentrations should be normal in patients with creatine transporter defects.

### ● *AGAT Deficiency*

Recently the first two cases with AGAT deficiency have been described [16]. In two Italian female siblings with mental retardation, in vivo magnetic resonance spectroscopy disclosed severe creatine deficiency in the brain [17]. The significant increase of brain creatine levels upon oral creatine substitution is similar to observations in the patients with GAMT deficiency when treated with oral supplements of creatine-monohydrate, but GAMT deficiency was excluded by low urinary and plasma guanidinoacetate concentrations and by normal GAMT enzyme activity as measured in cultured skin fibroblasts and virus-transformed lymphoblasts. AGAT enzyme activity was under the level of detection in the EBV-transformed lymphoblasts of these patients.

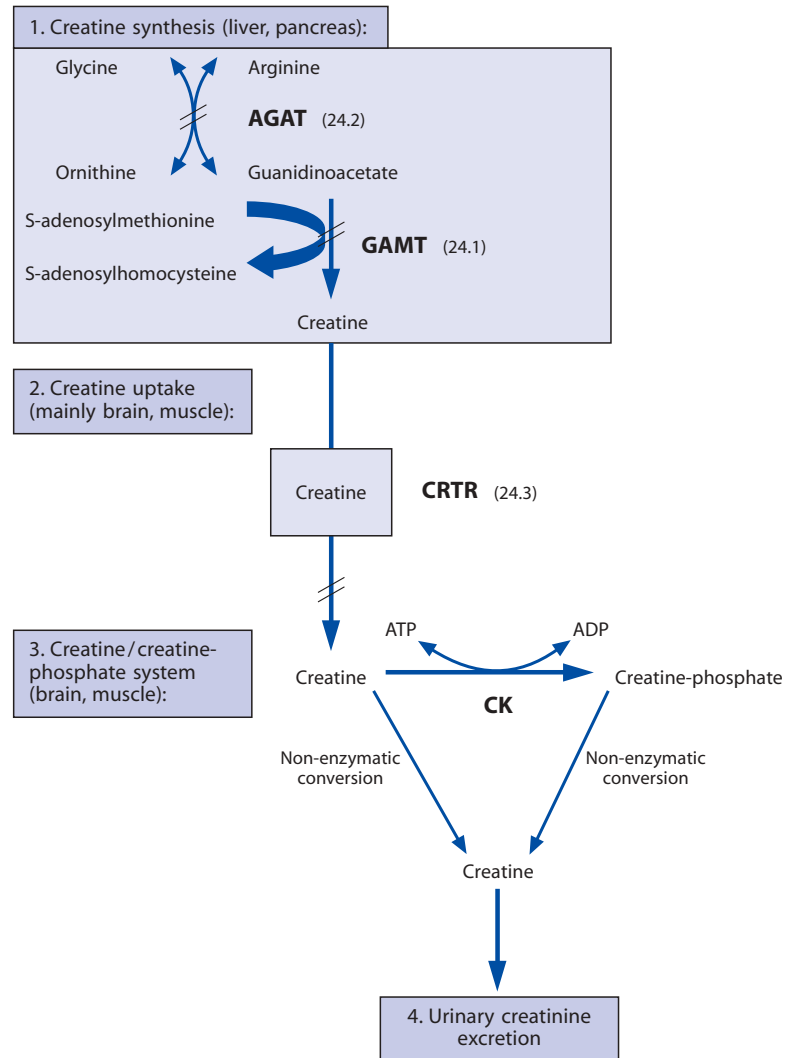
### ● *Creatine Transporter Deficiency*

Recently, a 6 year old patient with a putative creatine transporter deficiency has been reported [18]. Clinically, this patient had general developmental and speech delay since early childhood, epileptic seizures, a pathologic EEG and non-specific signal alterations in T2- weighted MR images of the brain. Guanidinoacetate concentrations in this patient's body fluids (plasma, urine) were within normal range, while creatine concentrations were elevated in urine and plasma. Brain creatine levels, as determined by in vivo magnetic resonance spectroscopy, were extremely low. In contrast to GAMT and AGAT deficiencies, there was virtually no increase in brain creatine concentrations upon high dosage oral creatine substitution. Biochemical and molecular genetic investigations have confirmed that this patient and his family suffer from an X-linked creatine transporter syndrome as a result of a hemizygous nonsense mutation in the SLC6A8 gene [19]. The genomic sequence of this gene has been determined and mapped to the X-chromosome distal to G6PD in Xq28 [20, 21]. Another creatine transporter locus has been identified on chromosome 16p11.2 [21].

## 24.2 Nomenclature

No.	Disorder affected component	Diagnostic tissue distribution	Chromosomal localisation	MIM
24.1	Guanidinoacetate methyltransferase (GAMT) deficiency	Liver; virus-transformed lymphoblasts; cultured fibroblasts; cultured amniocytes	19p13.3	601240
24.2	L-Arginine:glycine amidinotransferase (AGAT) deficiency	Liver; kidney; lymphoblasts; cultured fibroblasts	15	602360
24.3	Creatine transporter (Cr1) deficiency (CRTR)	Brain; muscle; virus-transformed lymphoblasts; cultured fibroblasts	Xp28	300036

### 24.3 Metabolic Pathway



**Fig. 24.1.** Metabolic pathway of creatine/creatine-phosphate. *AGAT*, arginine:glycine amidinotransferase; *GAMT*, guanidinoacetate methyltransferase; *CRTR*, creatine transporter; *CK*, creatine kinase

## 24.4 Signs and Symptoms

**Table 24.1.** Guanidinoacetate methyltransferase (GAMT) deficiency, n=15

System	Symptoms/markers	Neonatal <sup>a</sup>	Infancy	Childhood	Adolescence <sup>b</sup>	Adulthood <sup>b</sup>
Characteristic clinical findings	Developmental delay	–	+	+	+	+
	Mental retardation	–	+	+	+	+
	Autistic behavior	–	+	+	–	–
	Speech delay	–	+	+	+	+
	Seizures	–	+	+	+ <sup>c</sup>	+ <sup>c</sup>
	Hypotonia	–	+	±	–	–
	Extrapyramidal/ pyramidal signs	–	±	±	+	+
	MRI: abnormal signal intensity/basal ganglia	?	±	±	+	+
	EEG: slow background activity, epileptic dis- charges	?	+	+	+	+
Special laboratory	Guanidinoacetate (P, U, CSF)	↑	↑	↑	↑	↑
	Creatine (P, U, CSF)	n↓	↓	↓	n.d.	n.d.
	Creatinine (P, U)	n↓	n↓	↓	↓	↓
	GAMT-activity (EBV-transformed lym- phoblasts, FB)[22]	↓	↓	↓	↓	↓
In vivo <sup>1</sup> H and <sup>31</sup> P spectroscopy (brain)	Total creatine/ phosphocreatine	n↓	↓	↓	↓	↓
	Guanidinoacetate/phos- phoguanidinoacetate	↑	↑	n.d.	n.d.	n.d.

<sup>a</sup> Anamnestic clinical data and retrospective investigation of analytes in preserved dried filter paper samples.

<sup>b</sup> Data available only from 2 siblings [13].

<sup>c</sup> Eyelid myoclonia with absences (EMA), drug-resistant [13].

n.d., Not detectable.

**Table 24.2.** Arginine:glycine amidinotransferase (AGAT) deficiency, n=2 [16]

System	Symptoms/markers	Infancy	Childhood
Characteristic clinical findings	Developmental delay	+	+
	Mental retardation	+	+
	Speech delay	+	+
	Seizures	(+)	+
	MRI: abnormal signal intensity/basal ganglia	–	–
	EEG abnormalities	(±)	(±)
Special laboratory	Guanidinoacetate (P, U, CSF <sup>a</sup> )	↓	↓
	Creatine (P, U, CSF <sup>a</sup> )	n↓	n↓
	Creatinine (P, U)	n↓	n↓
	AGAT-activity (EBV-transformed lymphoblasts)	↓	↓
In vivo <sup>1</sup> H and <sup>31</sup> P spectroscopy (brain)	Total creatine/phosphocreatine	↓	↓

<sup>a</sup> CSF: no data available for patients so far.

**Table 24.3.** Creatine transporter (CRTR) deficiency, data refer to the only (6 year old) patient known so far [18]

System	Symptoms/markers	Childhood
Characteristic clinical findings	Moderate developmental delay	+
	Speech delay	+
	Seizures	+
	Hypotonia	+
	Increased head circumference	+
Analytes	Guanidinoacetate (P, U)	n
	Creatine (P, U)	n-↑
	Creatinine (P, U)	n
In vivo $^1\text{H}$ and $^{31}\text{P}$ spectroscopy (brain)	Total creatine/phosphocreatine	↓

## 24.5 Normal and Pathological Values

**Table 24.4.** Urinary excretion of creatinine

Age (yr)	Normal values creatinine [23, 24]		Patients with GAMT deficiency	
	$\mu\text{mol}/24\text{ h}$	$\mu\text{mol}/\text{kg}/24\text{ h}$	$\mu\text{mol}/24\text{ h}$	$\mu\text{mol}/\text{kg}/24\text{ h}$
		Male      Female		
0–1	221–1 326			
1–2	619–1 768	70.7–176.8	106–159.1 [14]	8.8–12.3 [14]
2–3	884–2 652	87.5–131.7		24.7 [11]
3–4	884–2 652			
4–5	884–2 652	87.5–131.7		25.6 [11]
4–6	3 200	185.6		38–45.9 [25]
6–8	4 570	187.4		
8–10	5 649	202.4		
10–12	7 152	202.4		
12–14	8 814	204.2		
14–16	11 846	222.7		
16–18	13 967	232.4		

**Table 24.5.** Guanidinoacetate, creatine and creatinine in 24.1 GAMT deficiency

Compounds	Material	Cation-exchange chromatography [14] (μmol/l)	GC/MS [11, 26] (μmol/l)	Tandem mass spectrometry TMS [27]		
				(μmol/l)		
				Newborn	Children (5–10 years)	Adult
Normal values						
GAA	U	63.4–429	10–99 <sup>a</sup>			
	P	0.832±0.315	0.65–1.4		3.91±0.76	5.02±1.84
	dBS			4.83±1.43		5.04±1.17
	CSF	0.055±0.032	0.046–0.182			
	AF		2.7–4.4			
Creatine	U	46–5,250				
	P	86.9±18.5			58.96±22.30	34.7±15.26
	CSF	38.8±4.76				
Creatinine	U	1800–4400				
	P	20.2±7.49				
	CSF	34±5.59				
Pathological values						
GAA	U	2224–3987	453–5139 <sup>a</sup>			
	P	12.9–20.7	20.9–38.4		11.57–15.16	
	CSF	10.6–12.7	13.7–15.2			
	AF					
Creatine	U	56.9–106				
	P	0.39–1.24			5.37–8.15	
	CSF	0.280–0.530				
Creatinine	U	1060–2060				
	P	3.33–5.21				
	CSF	<1.0				

TMS, tandem mass spectrometry; GC/MS, gas chromatography/mass spectrometry; GAA, guanidinoacetate; U, urine; P, plasma; dBS, dry blood spot; CSF, cerebrospinal fluid; AF, amniotic fluid.

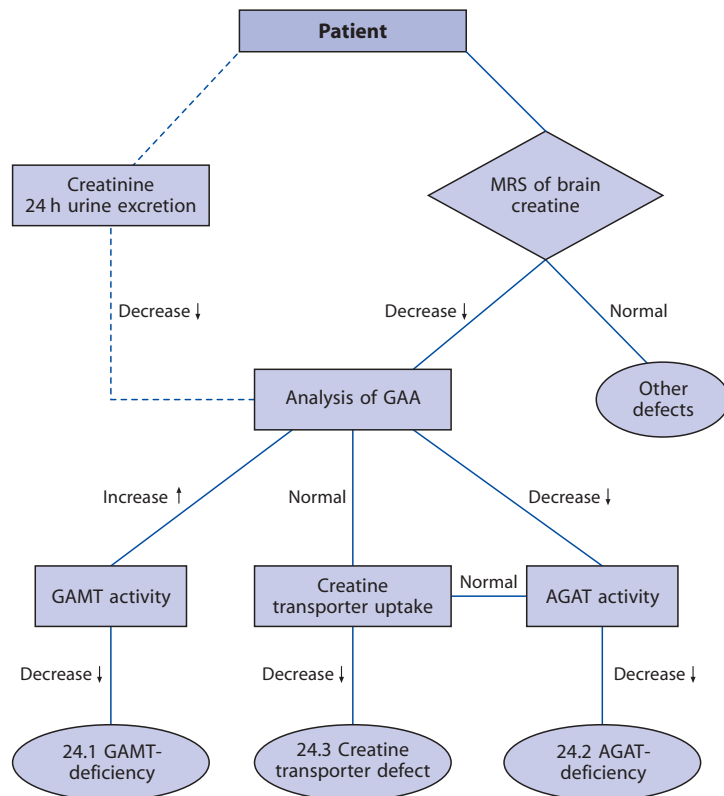
<sup>a</sup> mmol/mol creatinine.

## 24.6 Loading Test

Not applicable.



## 24.7 Diagnostic Flow Chart



**Fig. 24.2.** Diagnostic flow chart for the patient with creatine biosynthesis and cellular creatine transporter defect. Starting points are clinical symptoms and/or finding of ↓ MRS brain creatine/creatinephosphate

## 24.8 Specimen Collection

Test	Preconditions	Material	Handling	Pitfalls
Creatinine	Before creatine supplementation	U	24 h urine	Low levels in patients with reduced muscle mass
		CSF P	Store at $-20^{\circ}\text{C}$ 2 ml, EDTA tubes	Probably not diagnostic in neonates
GAA		U	Room temp.	
		CSF P	Store at $-20^{\circ}\text{C}$ 2 ml, EDTA tubes	
Creatine	Before creatine supplementation	dBS	Room temperature	Probably not diagnostic in neonates
		CSF	Store at $-20^{\circ}\text{C}$	
GAMT, AGAT, CRTR activity		P	2 ml, EDTA tubes	
		Liver	Store at $-80^{\circ}\text{C}$	
		FB Lymphoblasts	Cultured skin cells EBV transformed	

dBS, dry blood spot; FB, fibroblasts.

## 24.9 Prenatal Diagnosis

Disorder	Method/analytes	Material	Timing, trimester
24.1	Mutation analysis	CV, cultured amniotic cells	I, II
	GAA	AF	II
	GAMT-activity	Cultured amniotic cells <sup>a</sup>	I, II
24.2	Mutation analysis	CV, cultured amniotic cells	I, II
	AGAT-activity	Cultured amniotic cells <sup>a</sup>	II
24.3	Mutation analysis	Amniotic and chorionic cells	I, II

Prenatal diagnosis has not been performed for disorders 24.1, 24.2 and 24.3.

<sup>a</sup> More than two 75 cm<sup>2</sup>-flasks are needed for GAMT/AGAT-activity measurement, therefore prenatal diagnosis is not practicable.

## 24.10 DNA Analysis

Disorder	Tissue	Methodology	Mutations
24.1	Genomic DNA (cultured FB, EBV-transformed lymphoblasts, LYM, dBS) [28–30]	PCR, DGGE, direct sequencing	Splice-site (exon 2), insertions (exons 1, 2, 5), deletion (exon 2/intron 2), transversion (intron 5), transition (exons 4, 6)
24.2	Genomic DNA (cultured FB, EBV-transformed lymphoblasts, LYM, dBS)	PCR, DGGE, direct sequencing	Nonsense (exon 3)
24.3	Genomic DNA (cultured FB, EBV-transformed lymphoblasts, LYM [19])	PCR, direct sequencing	Nonsense (exon 11)

PCR, polymerase chain reaction; DGGE, denaturing gradient gel electrophoresis; FB, fibroblasts; LYM, lymphocytes; dBS, dry blood spot.

## 24.11 Treatment

Disorder	Intervention	Creatine monohydrate [31]	Combination of	
			Arginine	Ornithine [25]
24.1	Oral dosis (g/kg BW/d) Effects: Creatine (P), 1 h Creatine/creatine-phosphate in brain (MRI), Creatinine (U) Guanidinoacetate	0.35–2  ↑ 90%–n  n ↓ <sup>a</sup>	  a a  a ↓	  a a  a ↓
24.2	Oral dosis (g/kg BW/d)	0.35–2		

<sup>a</sup> No influence; no treatment available for disorder 24.3 so far.

## 24.12 Summary

According to the creatine pathways in the body, two main categories of disorders in creatine metabolism can be expected: disorders in creatine synthesis, and disorders of cellular creatine transport.

GAMT deficiency is the first inborn error of creatine metabolism clinically characterised by mental retardation, epilepsy, and extrapyramidal

symptoms. Characteristic biochemical findings include brain a creatine deficiency which is completely reversible upon oral creatine supplementation, and accumulation of guanidinoacetate in brain and in body fluids.

Recently two new creatine deficiency syndromes (AGAT and CRTR deficiency) have been described: AGAT deficiency is characterised by a cerebral creatine deficiency which is reversible upon oral creatine substitution and by low levels of guanidinoacetate in body fluids. A CRTR deficiency is mainly characterised by a cerebral creatine deficiency which is not reversible upon oral creatine substitution and by normal or elevated creatine concentrations in plasma and urine.

According to the limited number of patients identified so far, the clinical spectrum of GAMT, AGAT and CRTR deficiencies includes mental retardation as main symptom. Further recognition of patients with defects in creatine synthesis will be of major importance as affected patients may substantially benefit from oral creatine substitution. Determination of guanidinoacetate, creatine and creatinine in body fluids and determination of brain creatine by in vivo magnetic resonance spectroscopy are valuable diagnostic tools.

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