REVIEW

Human guanidinoacetate n-methyl transferase (GAMT) deficiency: A treatable inborn error of metabolism

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Abstract: The creatine biosynthetic pathway is essential for cellular phosphate associated energy production and storage, particularly in tissues having higher metabolic demands. Guanidinoacetate N-Methyl transferase (GAMT) is an important enzyme in creatine endogenous biosynthetic pathway, with highest expression in liver and kidney. GAMT deficiency is an inherited autosomal recessive trait that was the first among creatine deficiency syndrome to be reported in 1994 having characteristic features of no comprehensible speech development, severe mental retardation, muscular hypotonia, involuntary movements and seizures that partly cannot be treated with anti-epileptic drugs. Due to problematic endogenous creatine biosynthesis, systemic depletion of creatine/phosphocreatine and accumulation of guanidinoacetate takes place that are the diagnostic features of this disease. Dietary creatine supplementation alone or along with arginine restriction has been reported to be beneficial for all treated patients, although to various extent. However, none of the GAMT deficient patient has been reported to return to complete normal developmental level.

Keywords: CDS; GAMT deficiency; creatine/phosphocreatine system; guanidinoacetate; mental retardation.

INTRODUCTION

**Creatine phospho creatine energy shuttle**
Creatine (Cr) and Phospho creatine (PCr) system provides an instant energy source of high-energy phosphate and serves as ATP derived energy reservoir (Iqbal et al., 2015). It is also involve in energy transport from production site, in mitochondria, to the consumption sites, such as muscles and brain due via active sodium dependent creatine transporter (Guimbal and Kilimann, 1993; Sora et al., 1994; Iqbal et al., 2011). Most of creatine in body comes through diet as well as it can be synthesized endogenously in liver and pancreas by using glycine and arginine as substrates and Arginine: Glycine Amidino Transferase (AGAT) and Guanidinoacetate N-Methyl Transferase (GAMT) as the catalyst Iqbal, 2009). AGAT is responsible for the reversible transport of amidino group from arginine to glycine yielding ornithine and guanidinoacetate (GAA). Methylation of GAA, catalyzed by GAMT, results in the production of creatine (Cr) and S-adenosyl-L-methionine (SAM) converts into S-adenosyl-L-homocysteine after donating its methyl to GAA (Schulze, 2003). In Cr storing tissues, Creatine Kinase (CK) mediates Phosphorylation/depshorylation of Cr and thus provides a high-energy phosphate buffer during ATP synthesis and utilization (Battini et al., 2006). Ultimately, Intracellular Cr and phosphocreatine (PCr) are non-enzymatically cycled to creatinine (fig. 1). This conversion has a constant daily turnover of 1.5% of total body creatine. Creatinine is mainly excreted in urine and daily urinary creatinine excretion is directly proportional to total body creatine concentration (Bianchi et al., 2000).

**Creatine deficiency syndrome (CDS)**
Despite its critical importance, until 1994, no primary metabolic disorders of creatine synthesis and transport were identified. Stöckler et al. (1994) had reported the first case of GAMT deficiency. X-linked inherited alteration of creatine metabolism was second among CDS to be reported in 2001 in two pedigrees having central nervous system with disturbed creatine transporter 1 (Cecil et al., 2001; Salmons et al., 2001). Finally in 2001, two Italian sisters, having a previously unclassified brain Cr deficit, were confirmed by Item et al. (2001). to be suffering from AGAT deficiency

**Biochemical and molecular characterization of GAMT**
GAMT is believed to be the major enzyme involved in the metabolic conversion of SAM to SAH and the endogenous biosynthesis of Cr is reported to represent 75% of the total utilization of methionine through SAM in human beings (Mudd et al., 1980). GAMT is responsible for the SAM dependent methylation of GAA to yield Cr and SAH. Maximum GAMT expression is reported in kidney, liver and pancreas (Braissant et al., 2001) and also detected in lower extents in brain (Stöckler et al., 1996; Braissant et al., 2008), lymphocytes and fibroblasts (Mudd et al., 1980). It has been demonstrated that most SAH dependent methyltransferases including GAMT are inhibited by SAH (Lion et al., 2006). The remaining methyl groups are used for DNA, protein and other methylation reactions (Wyss and Kaddurah-Daouk, 2000).

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GAMT gene consists of 6 exon and mapped to chromosome 19p13.3 (Schulze, 2003). GAMT protein has α/β open sandwich structure and its 1-42 residues in N-terminal section covers the active site entrance, hence making it unavailable for reaction. To open the active site entrance, N-terminal section moves through Brownian motion and SAM along with GAA molecules enters and binds firmly to their respective sites by hydrogen bonds and to get excluded from the active site, unbound water molecules (Komoto et al., 2004).

Human GAMT deficiency; Clinical manifestation
GAMT deficiency is an inherited autosomal recessive disorder. Around 50 cases of human GAMT deficiency has been reported, till now from all over the world, since its discovery in 1994 (Van der Knapp et al., 2000; Leuzzi, 2002; Stöckler et al., 1997; Schulze et al., 1997; Dhar et al., 2009). The pathophysiology of GAMT deficiency may involve neuromodulatory and/or neurotoxic action of GAA, which is a partial agonist at GABA receptors (Neu et al., 2002).

GAMT deficiency has heterogeneous clinical presentations. However, generally developmental delay which is observed at 6 to 12 months of age along with/or developmental arrest in the second year of life, no active or comprehensible speech development, muscular hypotonia, dyskinetic involuntary movements, severe mental retardation and seizures, which partially can not be treated by anti-epileptic drugs, are considered as characteristic features of this disease. In older patients, autism with self injurious behaviour has been reported by Item et al. (2004). Intensive extra pyramidal movement disorder and epilepsy are common features observed in patients with a severe phenotype of the disease. Whereas only show developmental delay and mild epilepsy has been reported in mildly affected patients (Stromberger et al., 2003).

Human GAMT deficiency; Diagnostic findings
Impaired de novo creatine biosynthesis results in systemic depletion of Cr and PCr and is the hallmark of GAMT deficient patients. In vivo proton magnetic resonance spectroscopy has shown that extremely low brain Cr concentrations may explain the persistence of epilepsy, dyskinetic, seizures, social contact, alertness and behaviour is commonly observed in the first few months after initiating Cr treatment. Cr/PCr concentration increases the Cr/PCr concentration in the brain. However, generally prolonged supplementation is required (Bodamer et al., 2009). The clinical course is timely correlated with the observed changes of Cr/PCr in the brain. However, further clinical improvement, thereafter delays, especially in patients with the severe phenotype, therapy refractory seizures reoccur and the clinical circumstances may deteriorates (Schulze et al., 1997).

Oral supplementation with 0.35-2.0g/day of Cr slowly increases the Cr/PCr concentration in the brain. However, even after several months, Cr/PCr in these patient’s brain remains significantly below the normal brain ranges (Bodamer et al., 2001). Cr replacement also causes decreased GAA formation in GAMT deficient patients as GAA concentrations are reported to remain largely elevated in cerebrospinal fluid, serum and urine of these patients (Schulze et al., 2001). These high GAA concentrations may explain the persistence of epilepsy, one of the common features of the disease (Bodamer et al., 2009).

It has been reported that a significant and permanent decrease of GAA in body fluids of some GAMT deficient patients has been observed following dietary arginine restriction (15mg/Kg/day) in combination with ornithine supplementation (100mg/Kg/day) (Schulze, 2003). These subjects showed marked clinical improvement including...
distinctly reduced epileptogenic activities accompanied by almost complete disappearance of seizures and demonstrates the positive effect of GAA reduction in these patients (Schulze et al., 2001).

**CONCLUSION**

GAMT deficiency is a rare recessive metabolic disorder in which endogenous creatine synthesis is compromised. Dietary creatine supplementation alone or along with arginine restriction has been reported to be beneficial for all treated patients, although to various extent. However, none of the GAMT deficient patient has been reported to return to complete normal developmental level.

**REFERENCES**


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