A Case of Guanidinoacetate Methyltransferase (GAMT) Deficiency

Case History

A female patient was born at term to non-consanguineous parents. There were no neonatal problems. Birth weight (3.3kg) and head circumference (33cm) were normal and there were no dysmorphic features. There was no family history of suspected metabolic disorders.

The patient presented at 10 months with failure to thrive. On observation weight and head circumference had fallen to below the 2nd centile and there was marked truncal hypotonia and global developmental delay (e.g. unable to sit unaided). There were no obvious dysmorphic features and hearing, vision and reflexes were all normal. Feeding difficulties included aspiration, reflux and the inability to tolerate solid feeds. Feeds were at first given through a nasogastric tube and then she was fed predominantly via a gastrostomy. At 12 months she developed fitting and seizures which were severe and frequent. Although she showed some response to clonazepam occasional myoclonic seizures persisted.

An MRI scan performed at this time, revealed a bilateral symmetrical high signal in the globus pallidus and an abnormal signal change in the basal ganglia, which was felt to be non-specific but suggestive of ischaemic, metabolic or degenerative changes. The myelination pattern was normal.

Preliminary Laboratory Investigations

Initial routine biochemical investigations (U+E's, LFTs, Bone profile and TFT's) were all normal. Ammonia was slightly elevated at 80 μmol/L (Ref : 5 – 60). Serum lactate was raised on three occasions at 5.9, 4.3 and 3.3 mmol/L (Ref : 0.6 – 2.4), however CSF lactate was within the normal range. Urine organic acids and acyl carnitines were normal. Other metabolic investigations, including urine reducing substances, urine amino acids, plasma VLCFA, leucocyte lysosomal enzymes and karyotyping were performed. However, with the exception of a generalised aminoaciduria, these showed no abnormalities.

Differential Diagnosis

At this stage the possibility of a respiratory chain disorder was suspected due to the raised serum lactate level (although CSF levels were normal) coupled with the encephalopathy and MRI changes.

Recommended Further Investigations

Skin and muscles biopsies were taken to investigate the possibility of a respiratory chain disorder. A muscle biopsy showed mild lipid and glycogen accumulation. Cytochrome oxidase staining was normal. Respiratory chain studies revealed evidence of **complex I deficiency in muscle.** Results in fibroblasts were similar. Muscle mtDNA analysis was negative for all known mitochondrial mutations.

	Muscle	
	Patient	**Controls (n=8)**
Complex I	**0.052**	0.166 ± 0.047
Complex II	0.125	0.208 ± 0.070
Complex IV	1.496	1.805 ± 0.550
Complex I : Complex II	**0.342**	0.817 ± 0.153

Activities expressed as ratios to citrate synthase activity except for the bottom row in which complex I activity is expressed as a ratio to complex II activity.

These results together with the MRI findings, clinical symptoms and raised lactate led, at 12 months of age, to a diagnosis of a Leigh-like Syndrome due to a Complex I deficiency..

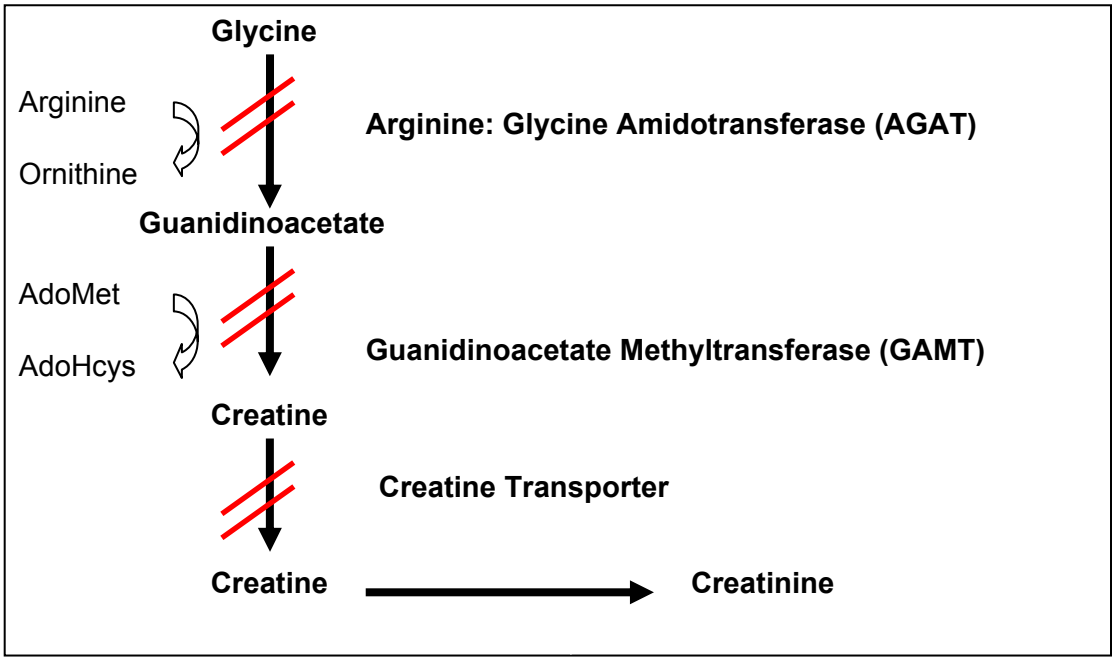
Results of Further Testing

Eight months after the initial diagnosis the patients was referred for nephrological review due to hypomagnesamia requiring supplements. There was no tubular nephropathy and plasma magnesium had been slightly reduced on only one occasion. However urine magnesium/creatinine and calcium/creatinine ratios were very high. After further investigation it was felt that these apparently elevated ratios were secondary to a very low urine creatinine (0.1 mmol/L). The 24 hour urine creatinine excretion was measured as 5 μ mol/kg/24hours (Ref. 71 - 177). Looking back over biochemistry results the plasma creatinine had always been low / low normal with results varying between 9 and 20 μ mol/L (Ref. 16 - 41). Low levels of urinary creatinine would also account for the apparent generalised aminoaciduria when levels are expressed as ratios to creatinine excretion.

A diagnosis of **Guanidinoacetate Methyltransferase (GAMT) Deficiency** in this patient was confirmed by the finding of a highly elevated guanidinoacetate in urine (28091 mmol/mol creatinine; Ref: 10-100) and undetectable GAMT activity in lymphocytes. The patient was found to be a compound heterozygote for two GAMT alleles, a common mutation affecting a splice site (327G>A) and a novel mutation creating a stop codon (522G>A).

Overview of the Disease

GAMT deficiency is a disorder of creatine synthesis[1]. Creatine is excreted by non-enzymatic conversion to creatinine and the excretion of creatinine is directly proportional to the total body creatine. The metabolic pathway of creatine synthesis, which occurs mainly in the liver, is shown below. There are three known defects in the pathway – two synthesis defects, AGAT deficiency and GAMT deficiency and an X-linked transporter defect affecting the cellular uptake of creatine in the brain.



(Adomet = S-Adenosylmethionine; AdoHcys = S-Adenosylhomocysteine)

GAMT deficiency, the most severe of the disorders, was the first inherited disorder of creatine metabolism to be described in a case published by Stockler in 1994[2]. Symptoms include psychomotor retardation-particularly affecting speech, hypotonia, seizures and a movement disorder.

The severe depletion of creatine and phosphocreatine in the brain can be detected by proton magnetic resonance spectroscopy (MRS). This technique however has limited availability and requires specialist interpretation. Diagnosis is therefore often based upon the detection of increased amounts of guanidinoacetate and low creatine in the plasma and urine. This requires highly sensitive and accurate methods such as stable isotype dilution MS, HPLC and TMS. The enzyme activity can also be measured in lymphocytes, and mutation analysis for the common alleles is available.

Treatment and Monitoring

Although the role of creatine in the brain is not completely understood, the pathogenesis of GAMT deficiency appears to be at least in part due to the depletion of creatine in the brain. In addition, the accumulation of GAMT may have a toxic effect specific to GAMT which does not occur in the other disorders of creatine synthesis. Although muscle tissue may be another site of creatine depletion patients have not shown pronounced cardiac or skeletal myopathy.

Patients with GAMT and AGAT deficiency benefit from supplementation with creatine / creatine monohydrate. This treatment is not effective in the transporter defect. Creatine supplements have been shown to increase serum and urine creatinine, reduce guanidinoacetate and replenish brain creatine resulting in improvement on MRI. Patients have shown improved development and muscle tone and reduced seizures; however none have yet achieved normal development.

This patient was started on creatine supplements following diagnosis and within 9 months had made developmental progress with improvements in both fine and gross motor skills. Seizures resolved, except during a febrile illness, and a repeat MRI showed near resolution of abnormalities. Plasma creatinine was 42 μ mol/L. The patient is now 7 years old and although has made some progress she remains severely handicapped, has developed no meaningful language and has poor concentration. She is fed predominantly through a gastrostomy and is doubly incontinent.

It has been suggested that a low arginine diet, supplemented with ornithine may also have a role in treatment by reducing the accumulation of guanidinoacetate which itself may act as a neurotoxin. Ornithine has a direct inhibitory effect on AGAT, and by reducing arginine concentrations pushes the reaction towards glycine. Dietary treatment has been tried in this patient with some effect. At 6 years of age she was started on a diet of no natural protein, an arginine free essential amino acid mix (0.65g/kg/day) and ornithine supplements (100 mg/kg/day). Arginine levels decreased remaining stable at the lower limit of the reference range. Although the plasma guanidinoacetate levels remained high there was a decrease from 14.7 μ mol/L to 4.67 μ mol/L (Ref. 0.35-1.8) over a 6 month period, coupled with a perceived improvement in the patient's development. There is no clinical or biochemical evidence of protein malnutrition.

The long term prognosis is as yet unclear due to the small number of patients with the condition. It is possible in the future that early treatment may prevent the development of severe symptoms.

GAMT Deficiency and Mitochondrial Function

This patient has a confirmed diagnosis of GAMT deficiency but also had abnormalities in the respiratory transport chain. There are two hypotheses to consider as to why this association may occur. Either GAMT deficiency decreases creatine therefore causing secondary changes due to an effect on ATP metabolism (creatine phosphate maintains ATP levels due to its high phosphoryl transfer potential) or there is a direct toxic effect of GAMT on the respiratory transport chain. Respiratory chain studies have been carried out in two previous patients with GAMT deficiency. One was found to have increased activity of complexes I, III and V in fibroblasts[3] and the other decreased ATP production with normal complex activity. This patient has decreased activity, providing further evidence that secondary abnormalities of the respiratory transport chain can occur in GAMT deficiency. It is unlikely with non-consanguineous parents, but not impossible, that this patient has two metabolic disorders.

Summary

- This case highlights the importance of routine biochemical tests in picking up an unusual inborn error. In this case low urine creatinine led to spuriously high concentrations of urinary metabolites that led to a false diagnosis of a renal tubular problem. The consistently abnormally low or borderline plasma and urine creatine concentrations were a clue to the diagnosis.
- GAMT deficiency may be significantly under diagnosed as symptoms mimic other metabolic diseases and the critical metabolites are not routinely measured in most metabolic investigations.
- In this disorder there may be secondary defects of the respiratory transport chain which may lead to a misdiagnosis.
- GAMT deficiency is potentially treatable therefore an early diagnosis is important.
- The development of MRS for creatine and a wider availability of quantitative methods for creatine and guanidinoacetate are very important.

References

1 Stromberger et al. JIMD 2003, 26, 299-308
2 Stockler et al, Pediat Res 1994, 30(3), 409-413
3 Das, et al, JIMD 2000; 23:375-7
4 De Vries et al, JIMD 2005; 28 (suppl 1):227

Patient Confidentiality

Permission has been obtained for this case to be presented. The case was recently presented at the BIMDG annual meeting.