In humans and other mammals nitrogen is produced by the catabolism of proteins and excreted as urea via the kidneys through the process of the urea cycle\(^1\) (Figure 1). The urea cycle, which is active primarily in the liver, converts waste nitrogen into ammonium. Deficiencies of enzymes in the urea cycle may result in the accumulation of ammonium. Urea cycle disorders may present from infancy to adulthood.

**Urea cycle review**

The urea cycle consists of six enzymes and two mitochondrial membrane transporters (Figure 1): N-acetyl glutamate synthase (NAGS), carbamyl phosphate synthetase I (CPSI), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase, the aspartate transporter (citrin), and the ornithine transporter\(^1-3\). An interruption in any step of the urea cycle may cause a build-up of ammonium which is neurotoxic and if untreated may result in coma and death. All disorders except for X-linked OTC deficiency are inherited in an autosomal recessive manner. Enzymes located in the mitochondria are CPSI, NAGS, and OTC; these can therefore be affected by other mitochondrial diseases or perturbations. The incidence of urea cycle disorder (UCDs) in the United States is approximately 1 in 8200\(^4\). Prenatal testing based on mutation analysis is available for all six conditions\(^5-7\).

**ABSTRACT:** N-acetyl-glutamate synthase (NAGS) deficiency is a rare autosomal recessive urea cycle disorder (UCD) that uncommonly presents in adulthood. Adult presentations of UCDs include; confusional episodes, neuropsychiatric symptoms and encephalopathy. To date, there have been no detailed neurological descriptions of an adult onset presentation of NAGS deficiency. In this review we examine the clinical presentation and management of UCDs with an emphasis on NAGS deficiency. An illustrative case is provided. Plasma ammonia levels should be measured in all adult patients with unexplained encephalopathy, as treatment can be potentially life-saving. Availability of N-carbamylglutamate (NCG; carglumic acid) has made protein restriction largely unnecessary in treatment regimens currently employed. Genetic counselling remains an essential component of management of NAGS.

**RéSUMÉ:** Encéphalopathie récurrente : le déficit en NAGS (N-acétylglutamate synthase) chez l’adulte. Le déficit en N-acétyl-glutamate synthase (NAGS) est un désordre rare du cycle de l’urée (DCU) transmis de façon autosomique récessive qui survient rarement à l’âge adulte. Le mode de présentation des DCU chez l’adulte inclut des épisodes de confusion, des symptômes neuropsychiatriques et une encéphalopathie. À ce jour, il n’existe pas de description neurologique détaillée du mode de présentation du déficit en NAGS chez l’adulte. Dans cette revue, nous examinons le mode de présentation clinique et la prise en charge des DCU, particulièrement le déficit en NAGS, ainsi qu’une observation clinique. Les niveaux plasmatiques d’ammoniac devraient être mesurés chez tous les patients adultes présentant une encéphalopathie inexpliquée, étant donné que le traitement de cette pathologie peut leur sauver la vie. Depuis que le N-carbamylglutamate (NCG; acide carglumique) est disponible, il n’est plus nécessaire de restreindre l’apport en protéines chez ces patients. Le conseil génétique demeure une composante essentielle de la prise en charge du déficit en NAGS.
Clinical presentation of UCDs

The typical presentation for a urea cycle disorder occurs in the first few days of life. The infant may present with gastrointestinal symptoms such as vomiting occurring after feeding (protein load). Neurological symptoms such as lethargy, seizures and coma can follow quickly, a presentation identical to that of an infant with sepsis. A non-diagnostic work-up for sepsis should raise the clinical suspicion for an inborn error of metabolism. A common sign is hyperventilation and respiratory alkalosis as ammonium is a central nervous system (CNS) stimulant. Hyperventilation is thought to result from cerebral edema caused by the build up of ammonium; however hyperventilation can also be seen without evidence of cerebral edema. Neonates who present in the first few days of life do so as a result of the catabolic stress of labour and delivery and low fluid intake in the immediate post natal period.

Patients who have partial enzyme deficiencies, such as female carriers (X-linked OTC deficiency) will often have a delayed presentation despite a lifelong history of chronic cyclical nausea and vomiting, and possibly a seizure disorder or a psychiatric illness. There may also be developmental delay. Many patients self-select a low protein diet. In all groups of patients hyperammonemic crises may occur with increased catabolic stress caused by infection, starvation, surgery or trauma.

Approach to a patient with a suspected UCD

The approach to a patient considered to have a UCD includes a comprehensive neurological assessment with particular attention to family history and key clinical features such as behavioural changes, protein aversion and gastrointestinal symptoms. Investigations should first and foremost include an ammonia level. Other key investigations include arterial pH, serum lactate, serum glucose and cerebrospinal fluid (CSF) analysis, (with hyperammonemia there can be cerebral edema so CSF analysis should only be performed with caution) (Figure 2). It is important to note that hyperammonemia may be chronic or occur only during metabolic decompensation and therefore investigations can be normal. Electroencephalogram (EEG) (Figure 3) and magnetic resonance (MR) imaging can be helpful investigations. Fluid attenuated inversion recovery sequence (FLAIR) on MR imaging has been suggested to identify white matter tract abnormalities that can exist in UCDs. Other imaging techniques described to show abnormalities include diffusion tensor imaging (DTI) and MR spectroscopy. If plasma ammonia is elevated then metabolic indices such as plasma amino acids, urine orotic acid and urine organic acids should be measured. The importance of testing these metabolic indices is to differentiate among the various UCDs (Figure 4). A genetics and metabolic consultation is useful to proceed with further

Figure 1: Simplified version of urea cycle depicted. The urea cycle converts protein into urea which is excreted by the kidneys. There are six enzymes involved: N-acetylglutamate synthase (NAGS), carbamylphosphate-synthetase-I (CPSI), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase (ARG1). Further abbreviations: adenosine triphosphate (ATP), adenosine diphosphate (ADP). Redrawn with permission from: Lee B. Urea cycle disorders: Management. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA 2012. Copyright © 2012 UpToDate, Inc. For more information visit www.uptodate.com.


Figure 3: Electroencephalogram. Referential montage (common average reference) shows diffuse background slowing (delta) with the intermittent appearance of triphasic waves, with a bifrontal predominance.
work up for molecular analysis or tissue enzyme analysis. Patients suspected to be having a UCD should be managed in an intensive care setting as this is a medical emergency. Cerebral edema occurs early with severe hyperammonemia, and delays in reducing the level of ammonia may lead to serious neurological complications including death due to increased intracranial pressure with herniation. Survival from a severe episode often carries with it irreversible brain damage. Treatment should thus not be delayed if a UCD is suspected.

Medical and metabolic management

In an emergent presentation, physiologic stabilization is most important; adjunctive treatment may include intravenous fluids, and possibly hemodialysis for ammonia removal. The mainstay of ongoing management of NAGS deficiency, as with all UCDs is maintenance of plasma ammonia levels in a normal range by limiting protein intake, avoiding periods of catabolic stress, and using nitrogen scavenger drugs to allow an alternate pathway for the excretion of nitrogen precursors (e.g. sodium phenylbutyrate). Recently, in NAGS deficiency, specific treatment with carglumic acid, a structural analog of NAG has been used as it has been shown to activate CPSI and restore ureagenesis. Patients receiving carglumic acid typically do not require a protein restricted diet.

NAGS deficiency

N-acetylglutamate synthase (NAGS; MIM# 608300), one of the three mitochondrial enzymes of the urea cycle, produces N-acetylglutamate (NAG) from glutamate and acetyl coenzyme A (Acetyl CoA). N-acetylglutamate was first identified in the 1950’s and initially discovered as an intermediate in the arginine-biosynthetic pathway of Escherichia coli. N-acetyl glutamate synthase was later described as an essential allosteric cofactor of mitochondrial carbamylphosphate synthetase I (CPSI), the first enzyme of the urea cycle. N-acetyl glutamate synthase is primarily expressed in the liver and in the small intestine and its product, NAG, is postulated to activate CPSI. Hyperammonemia can result once CPSI is deprived of its co-factor NAG.

The first case report of NAGS deficiency was published in 1981 and subsequently approximately 34 other cases of NAGS deficiency have been reported with most patients presenting in the neonatal period. N-acetyl glutamate synthase deficiency is the least common UCD and few late-onset neurological presentations have been described; the gene mutation maps to chromosome 17q21.31. There are 22 published mutations up to date that have been described for NAGS.

Deficiencies of NAGS activity can either be inherited (mutation in NAGS gene) or acquired by a secondary inhibition of NAGS activity in some conditions which cause short chain fatty acid accumulation such as some organic acidemias and the use of valproic acid.

A detailed summary of published cases of NAGS in the literature is listed in the Table. Literature searches were done using online data bases such as PUBMED, GENE REVIEWS and OMIM. In total, 34 cases of confirmed NAGS deficiency were identified. This mini review will help with the understanding of the genetic aspects and key neurologic features associated with UCDs and therefore prompt earlier diagnosis and treatment. We discuss the unique presentation of an adult-onset UCD. Our patient had a history of behavioural change and confusion which is in keeping with a late-onset UCD. An adult presentation of NAGS deficiency however is very rare. No trigger was identified in our patient to account for his hyperammonemic crises.

Illustrative Case

The patient was symptomatic in early childhood and adulthood with symptoms of hyperammonemia in the setting of a negative family history although no ammonia level was checked until his hospitalization at age 38 years. A key clinical feature was an almost 20 year history of fluctuating behavioural changes associated with nausea and vomiting. A 38-year-old left-handed dairy farmer was referred for acute confusion and bizarre behavioural changes. His past medical history was notable for similar episodes dating as far back as 18 years. There had been no previous psychiatric or neurologic evaluation, however, a normal cranial computed tomogram (CT) scan had been reported. He was taken to the emergency room by his wife and upon assessment he described ongoing nausea and vomiting as well as headache. The patient had completed secondary school and two years of college with no history of learning difficulties. He was from a non-consanguineous Irish and Scottish background with no relevant family history.

On examination vital signs were stable. There was behavioural disinhibition and fluctuating drowsiness. A mini-mental status examination (MMSE) score was 23/30, (points lost for five-minute recall, three-step command, and constructing intersecting pentagons). Cranial nerve examination and power testing was normal. There was mild spasticity on assessment of muscle tone with brisk reflexes, sustained ankle clonus, and down-going plantar reflexes. Coordination was impaired.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis</th>
<th>Sex</th>
<th>Background History/Constitution</th>
<th>Clinical findings</th>
<th>Death</th>
<th>Peak Ammonia* Normal: 10-170 µmol/L</th>
<th>Glu on admission* Normal: 109-750 µmol/L</th>
<th>Clinical adenylate kinase* Normal: 10-50 µmol/L</th>
<th>Diagnosis by: enzyme analysis OR molecular studies</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3 months, female</td>
<td>Turk</td>
<td>Yes; older sister dead of severe hypotonia (NAGS deficiency not confirmed)</td>
<td>Asymptomatic</td>
<td>No</td>
<td>593</td>
<td>Ukn, but 19/01 on subsequent admission</td>
<td>Ukn</td>
<td>Second liver biopsy: reduced NAGS activity, later found to be homozygous for NAGS mutation</td>
<td>Gunel et al. Eur J Pediatr 2001; 109:197-199.</td>
</tr>
<tr>
<td>5</td>
<td>53 years, female</td>
<td>Ukn</td>
<td>Ukn</td>
<td>Ectopic abdominal mass with coma after caesarean section. Psychomotor seizures</td>
<td>No</td>
<td>130 - 681</td>
<td>Ukn</td>
<td>Ukn</td>
<td>NAGS deficiency on mutation analysis</td>
<td>Gundy et al. J Inherit Metab Dis 1991:51:566-574.2</td>
</tr>
<tr>
<td>9</td>
<td>9 weeks, male</td>
<td>Ukn</td>
<td>Yes; younger sister case 9</td>
<td>Recurrent vomiting, irritability, lethargy, later headaches, hallucinations</td>
<td>No</td>
<td>256</td>
<td>Elevated normal</td>
<td>Initially NAGS not assayed on liver biopsy</td>
<td>Later NAGS deficiency on mutation analysis</td>
<td>Caldicott et al. J Pediatr 2004;145:552-554.2</td>
</tr>
<tr>
<td>18</td>
<td>16 hours, male</td>
<td>Turk</td>
<td>Yes</td>
<td>Ectopic approximately 5 centimetre length</td>
<td>Yes</td>
<td>Ukn</td>
<td>Elevated normal</td>
<td>Post-mortem liver tissue: reduced NAGS activity Later parents found to be heterozygous</td>
<td>Caldicott et al. Hum Genet 2003;112:364-366.</td>
<td></td>
</tr>
</tbody>
</table>
Significant asterixis was present and gait assessment was normal. Otherwise general examination was unremarkable.

The patient was admitted to hospital. Extensive laboratory studies were all within normal limits. Magnetic resonance imaging of head and full-spine were reviewed with expert neuro-radiologists and deemed normal. Plasma ammonia was found to be markedly elevated at 434 μmol/L (15-55 μmol/L). A blood gas revealed a mild respiratory alkalosis. Continuous EEG monitoring (Figure 3) demonstrated severe generalized encephalopathy with associated triphasic waves suggesting metabolic or hepatic etiology with no epileptiform activity.

The patient responded well to intravenous fluids, lactulose and a relatively lower protein diet. Upon discharge plasma ammonia levels decreased to 85 μmol/L. A referral was made to a genetics/metabolics specialist to further investigate an underlying metabolic etiology.

A complete metabolic work-up revealed an elevated glutamine level of 1062 μmol/L (109-750 μmol/L), normal citrulline at 15 μmol/L (10-50 μmol/L), and normal urine amino acids. Urine orotic acid level was normal. On molecular studies OTC gene sequencing was normal (this was done as OTC deficiency is the most common UCD and orotic acid can be normal in OTC patients). Molecular sequencing of the NAGS gene was performed and the patient was found to be a compound heterozygote for E433G and IVS6+5 G > A, both novel mutations. The intronic mutation involved a consensus base pair located 5 bp downstream of an exon/intron boundary, in the donor splice site of intron 6. A G>A substitution in this position is expected to reduce efficiency of splicing of NAGS mRNA and lead to decreased, but not absent, expression of NAGS from this allele. The residual NAGS expression from this allele likely resulted in sufficient NAGS enzymatic activity to avoid neonatal hyperammonemia, and may serve to explain a delayed onset in adult life in our patient.

Mutation sequencing of NAGS was obtained in both parents. The patient’s father was confirmed to be a carrier of the IVS6+5 G > A mutation, but interestingly, no mutation was identified in the patient’s reported biological mother. Non-maternity, gonadal mosaicism or a de novo mutation may explain the absence of the E433G mutation in the mother.

Medical management of our case

A relatively low protein diet (around 1 gm/kg about <73 g/day) was commenced and our patient’s ammonia level was maintained in the normal range. Initially he was also started on sodium phenylbutyrate 200 mg/kg TID (4500 mg TID) and citrulline 50mg/kg TID (1200 mg TID). Sodium phenylbutyrate reduces ammonia production by creating an alternate pathway for the excretion of nitrogen containing precursors while citrulline also aids in nitrogen clearance and in maintaining the arginine pool in proximal UCDs.

Carglumic acid

Our patient was eventually switched to carglumic acid 1200 mg TID and a more liberalized protein intake once the diagnosis of NAGS deficiency was confirmed. The switch was made to carglumic acid because of non-compliance with a low-protein diet, intolerance to sodium phenylbutyrate and citrulline (stomach distress and body odour) and the specificity of
carglumic acid to NAGS deficiency. Carglumic acid activates CPSI therefore leading to a reduction in ammonia levels. Currently our patient’s ammonia levels are normal and range from 29-35 umol/L.

Carglumic acid is much more expensive than sodium phenylbutyrate (daily cost $1961.00 Canadian dollars for carglumic acid vs. $8.46 for sodium phenylbutyrate at current prices) however carglumic acid is the standard of care for patients with NAGS deficiency despite the cost, as treatment with scavengers and protein restriction are insufficient to prevent breakthrough hyperammonemia which would cause resultant increase in patient morbidity.25,26

Long-term management and morbidity

Our patient did eventually resume his work on the farm but remains troubled with mild short term memory loss. His behaviour has also shown a marked improvement. He has not had a hyperammonemic crisis for the last two years. His therapeutic course has been plotted (Figure 5).

Patients with UCD can present at any age and during hyperammonemic crises mortality can be as high as 10%.27 In chronic management, avoidance of periods of stress is important. Other neurologic sequelae of hyperammonemia may include seizures and/or developmental delay. Evidence suggests that virtually all survivors of a hyperammonemic coma are left with developmental delay.28-30 Cognitive impairment in adult-onset presentations has been described even in asymptomatic OTC-deficient heterozygous women (learning disabilities and attention deficit hyperactivity disorder).31,32 Although not specific to NAGS deficiency a recent review by Gropman et al33 does suggest that there is a neurochemical basis for cognitive and motor delay that may not only involve ammonia and glutamine as neurotoxins, but also alterations in the levels of neurotransmitters all leading to neuropathological changes. No specific literature exists regarding documenting cognitive deficits in adult-onset presentation of NAGS deficiency as it is a very rare condition.

CONCLUSIONS

Plasma ammonia should be measured in all patients with an unexplained encephalopathy including cyclical presentations to identify potential underlying metabolic disorders. Electroencephalogram can be a clue with the presence of triphasic waves indicating a metabolic encephalopathy. Hyperammonemia with a normal anion gap and normal serum glucose should be investigated to rule out a urea cycle disorder. Our illustrative case describes a rare presentation of a rare urea cycle disorder. Management for these patients requires a multidisciplinary approach including a dietician, social worker and a genetic counsellor. Awareness of inborn errors of metabolism presenting with neuro-psychiatric manifestations is essential for all adult neurologists and psychiatrists. Genetic counselling is an important component of UCDs management.

ACKNOWLEDGEMENTS

The authors thank the patient and family for giving us permission to share their information, Suzanne Ratko (dietitian) for her help with the nutritional management of the patient and Jill Tosswill (social worker) for her help with the social issues.

The NAGS mutation testing was done in Dr. Mendel Tuchman’s laboratory in Washington, DC.

REFERENCES


