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 (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 82004. Prenatal testing based on mutation analysis is available for all six conditions5-7.

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;\(^8\) 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\(^8\). 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\(^10\). 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\(^11\). 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 treatment.

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$^{12,13}$ (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$^{14-17}$ and restore ureagenesis$^{29}$. 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$^{19}$. N-acetyl glutamate synthase is primarily expressed in the liver and in the small intestine and its product, NAG, is postulated to activate CPSI$^{19}$. Hyperammonemia can result once CPSI is deprived of its co-factor NAG.

The first case report of NAGS deficiency was published in 1981$^{20}$ and subsequently approximately 34 other cases of NAGS deficiency have been reported with most patients presenting in the neonatal period$^{17}$. N-acetyl glutamate synthase deficiency is the least common UCD and few late-onset neurological presentations have been described$^{12,20-22}$; the gene mutation maps to chromosome 17q21.31$^{19}$. There are 22 published mutations up to date that have been described for NAGS$^{3,23}$.

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 behaviour changes associated with nausea and vomiting. A 38-year-old left-handed dairy farmer was referred for acute confusion and bizarre behaviour changes. His past medical history was notable 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</th>
<th>Clinical findings</th>
<th>Death</th>
<th>Gln on admission*</th>
<th>Diagnosis by: enzyme analysis OR molecular studies</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 months</td>
<td>male</td>
<td>Turkish</td>
<td>vomiting, feeding intolerance, episodic confusion</td>
<td>No</td>
<td>500</td>
<td>Ultrasensitive to ammonia, NAGS deficiency</td>
<td>Corne et al. Mol Genet Metab 2011; 104:279–282.</td>
</tr>
<tr>
<td>2</td>
<td>8 months</td>
<td>female</td>
<td>Turkish</td>
<td>Yes; older sister died of severe hypotonia (NAGS deficiency not confirmed)</td>
<td>asymptomatic</td>
<td>No</td>
<td>503</td>
<td>Ultrasensitive to ammonia, NAGS deficiency</td>
</tr>
<tr>
<td>5</td>
<td>33 years</td>
<td>female</td>
<td>Ultrasensitive to ammonia</td>
<td>epiglottic, abnorral nasal state, with coma after caesarean section, Psychomotor seizures</td>
<td>No</td>
<td>130–470</td>
<td>Ultrasensitive to ammonia</td>
<td>Grody et al. J Inherit Metab Dis. 1994;17(5):572–574.</td>
</tr>
<tr>
<td>13</td>
<td>3 days</td>
<td>male</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Haberle et al. Hum Mutat 2003;21(3):364–368.</td>
</tr>
<tr>
<td>14</td>
<td>3 days</td>
<td>male</td>
<td>Ultrasensitive to ammonia</td>
<td>Yes</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Haberle et al. Hum Mutat 2003;21(3):364–368.</td>
</tr>
<tr>
<td>15</td>
<td>4 days</td>
<td>male</td>
<td>Ultrasensitive to ammonia</td>
<td>Yes</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Haberle et al. Hum Mutat 2003;21(3):364–368.</td>
</tr>
<tr>
<td>16</td>
<td>3 days</td>
<td>male</td>
<td>Ultrasensitive to ammonia</td>
<td>Yes</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Ultrasensitive to ammonia</td>
<td>Haberle et al. Hum Mutat 2003;21(3):364–368.</td>
</tr>
<tr>
<td>18</td>
<td>16 hours</td>
<td>male</td>
<td>Ultrasensitive to ammonia</td>
<td>Febrile</td>
<td>IRD; arrested approximately 5 generations back</td>
<td>Not detected</td>
<td>ND</td>
<td>Post-mortem liver tissue: reduced NAGS</td>
</tr>
<tr>
<td>19</td>
<td>2 days</td>
<td>female</td>
<td>Ultrasensitive to ammonia</td>
<td>Negative</td>
<td>No</td>
<td>1300</td>
<td>1200</td>
<td>ND</td>
</tr>
<tr>
<td>20</td>
<td>2 days</td>
<td>female</td>
<td>Ultrasensitive to ammonia</td>
<td>Yes; younger sibling case</td>
<td>lethargy, anemia, vomiting, respiratory distress and seizures</td>
<td>No</td>
<td>178</td>
<td>170</td>
</tr>
</tbody>
</table>

**Table: Summary of findings in reported cases of confirmed N-acetylglutamate synthase (NAGS) deficiency**

- **Case**: Number identifying the case.
- **Age at diagnosis**: Age at diagnosis of the patient.
- **Sex**: Gender of the patient.
- **Background**: Background information about the patient.
- **Clinical findings**: Clinical findings associated with the patient.
- **Death**: Whether the patient died.
- **Gln on admission**: Gln on admission at the time of diagnosis.
- **Diagnosis by: enzyme analysis OR molecular studies**: Method used for diagnosing the patient.
- **Citation**: Reference for the case.

**Notes:**
- ND: Not detected.
- IRD: Intrauterine growth restriction.
- NAGS: N-acetylglutamate synthase.
- VPA: Valproic acid.
- CPS: Citrulline:proline synthetase.
- NAGS deficiency on mutation analysis: NAGS deficiency confirmed using cultured fibroblasts and DNA sequencing.
- Liver biopsy: L-Arginine unable to activate NAGS and normal CPS activity.
- Liver biopsy: No NAGS activity, later NAGS mutation found.
- Liver biopsy: reduced NAGS activity, NAGS mutation confirmed using cultured fibroblasts and DNA sequencing.
- Liver biopsy: NAGS activity reduced 25% control.
<table>
<thead>
<tr>
<th>Age</th>
<th>Days</th>
<th>Months</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Problems</th>
<th>NAGS Activity</th>
<th>Liver Function</th>
<th>Other Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4</td>
<td></td>
<td>female</td>
<td>Ukn</td>
<td>vomiting, hyperammonia, respiratory alkalosis</td>
<td>No</td>
<td>11/86</td>
<td>ND (Not Detectable)</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td></td>
<td>male</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hyperventilation, respiratory alkalosis</td>
<td>Yes</td>
<td>15/71</td>
<td>2 (Partial NAGS deficiency)</td>
</tr>
<tr>
<td>3-4</td>
<td>4</td>
<td></td>
<td>male</td>
<td>Ukn</td>
<td>agitation, trembling, seizures, hypotonia, anorexia</td>
<td>No</td>
<td>30</td>
<td>41 (Liver biopsy: NAGS activity &lt;40% of control)</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>history of lethargy and poor appetite</td>
<td>No</td>
<td>2010</td>
<td>30 (Liver biopsy: NAGS activity reduced to 97% of control)</td>
</tr>
<tr>
<td>3-5</td>
<td>2</td>
<td></td>
<td>male</td>
<td>Ukn</td>
<td>vomiting, hypotonia, visual impairment, persistent head and body shaking</td>
<td>No</td>
<td>185</td>
<td>755 (Liver biopsy: NAGS activity reduced to 40% of control)</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent seizures on mat. and mat.-labor, muscle stiffness on motor</td>
<td>No</td>
<td>5.15</td>
<td>Low (Liver biopsy: NAGS activity &lt;5% control)</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
<td></td>
<td>male</td>
<td>Taiwanese</td>
<td>Respiratory alkalosis</td>
<td>No</td>
<td>51</td>
<td>Low (Liver biopsy: NAGS activity &lt;50% control)</td>
</tr>
<tr>
<td>35</td>
<td>3</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>41</td>
<td>549 (Liver biopsy: NAGS activity &lt;10% control)</td>
</tr>
<tr>
<td>34</td>
<td></td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>111</td>
<td>940 (Liver biopsy: NAGS activity &lt;5% control)</td>
</tr>
<tr>
<td>31</td>
<td>5</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>250</td>
<td>850 (Liver biopsy: NAGS activity &lt;5% control)</td>
</tr>
<tr>
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<td></td>
<td>male</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>1054</td>
<td>940 (Liver biopsy: NAGS activity &lt;50% control)</td>
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<tr>
<td>33</td>
<td>13</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>940</td>
<td>1850 (Liver biopsy: NAGS activity &lt;10% control)</td>
</tr>
<tr>
<td>34</td>
<td>17</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>940</td>
<td>1850 (Liver biopsy: NAGS activity &lt;50% control)</td>
</tr>
<tr>
<td>33</td>
<td>5</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>940</td>
<td>1850 (Liver biopsy: NAGS activity &lt;10% control)</td>
</tr>
<tr>
<td>32</td>
<td>10</td>
<td></td>
<td>male</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>940</td>
<td>1850 (Liver biopsy: NAGS activity &lt;50% control)</td>
</tr>
<tr>
<td>31</td>
<td>15</td>
<td></td>
<td>female</td>
<td>Taiwanese</td>
<td>Persistent vomiting, hypotonia</td>
<td>Yes</td>
<td>940</td>
<td>1850 (Liver biopsy: NAGS activity &lt;10% control)</td>
</tr>
</tbody>
</table>

Ukn (unknown), LOC (loss of consciousness), CPS (carnosyl phosphate synthetase) mat. (maternal), EEG (electroencephalogram), VPA (valproic acid), Gln (Glutamine), Cit (Citrulline), ND (Not Detectable)
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 µmol/L.

Carglumic acid is much more expensive than sodium phenylbuturate (daily cost $1961.00 Canadian dollars for carglumic acid vs. $8.46 for sodium phenylbuturate 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 al.33 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 dietitian, 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

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References


