REVIEW ARTICLE

Recurrent Encephalopathy: NAGS (N-Acetylglutamate Synthase) Deficiency in Adults

A. Cartagena, A.N. Prasad, C.A. Rupar, M. Strong, M. Tuchman, N. Ah Mew, C. Prasad

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.

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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 mitchondrial 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].

From the Departments of Clinical Neurological Sciences (AC, ANP, MS), Paediatrics (ANP, CP), Children's Health Research Institute (ANP, CP), Biochemistry (CAR), University of Western Ontario, London. Ontario, Canada; Center for Genetic Medicine Research (MT), Center for Clinical an Community Research (NAM) Children's Research Institute, Children's National Medical Center, Washington DC, USA.

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Correspondence to: Chitra Prasad, Children's Hospital, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario, N6C 2V5, Canada. Email: Chitra.Prasad@lhsc.on.ca.

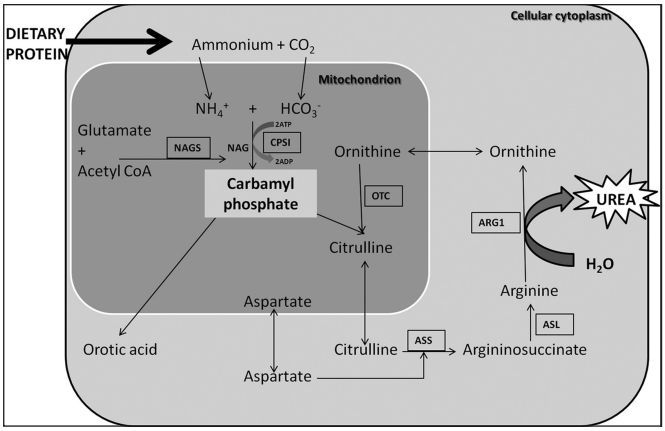

Figure 1: *Simplified version of urea cycle depicted. The urea cycle converts protein into urea which is excreted by the kidneys. There are six enzymes involved: N-acetylglutamate synthase (NAGS), carbamyl-phosphate-synthetase-I (CPSI), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), 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.*

- Complete blood count with differential
- Urinalysis
- Blood gases
- Serum electrolytes
- Liver enzymes and liver function tests
- Blood glucose
- **Plasma ammonia**
- Urine ketones if acidosis or hypoglycemia present
- Quantitative plasma and urine amino acids
- Urine organic acids
- Urine orotic acid
- Plasma lactate
- Carnitine (acyl and free)
- Acylcarnitine profile
- DNA for banking
- Liver biopsy for enzyme studies (now only rarely required due to easy availability of DNA based mutation studies)

Figure 2: *Recommended laboratory studies for a patient with a suspected inborn error of metabolism. Modified from Burton B. Inborn errors of Metabolism in Infancy: A Guide to Diagnosis. Pediatrics 1998;102(6):e69-e77.*

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[9]. 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

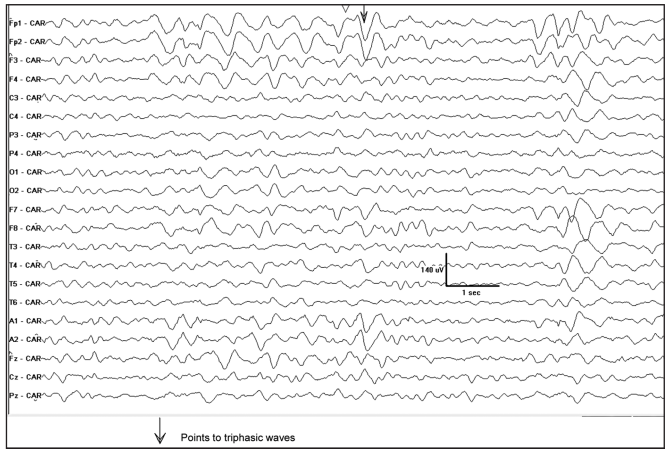

Figure 3: *Electroencephalogram. Referential montage (common average reference) shows diffuse background slowing (delta) with the intermittent appearance of triphasic waves, with a bifrontal predominance.*

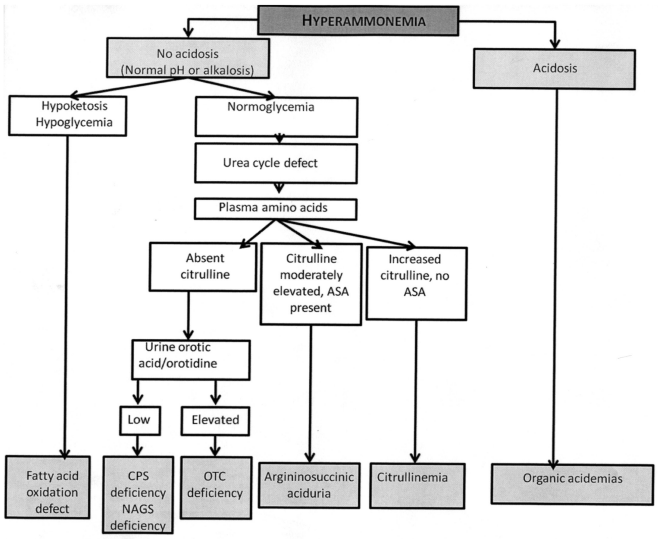

Figure 4: *Flow chart for the approach to hyperammonemia. Modified from Burton B. Inborn errors of Metabolism in Infancy: A Guide to Diagnosis. Pediatrics 1998;102(6):e69-e77., and Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr. 2001 Jan;138(1 Suppl):S30-9.*

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[2,9]. 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[18]. 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[2,20-22]; 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 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: Summary of findings in reported cases of confirmed N-acetylglutamate synthase (NAGS) deficiency

Case	Age at diagnosis; Sex	Background Consanguinity	Family History	Clinical findings	Death	Peak Ammonia* Normal <50 mmol/L	Gln on admission* Normal 109-750 mmol/L	Cit on admission* Normal 10-50 mmol/L	Diagnosis by: enzyme analysis OR molecular studies	Citation
1	6 male	Ukn	Ukn	vomiting, feeding intolerance, episodic confusion	No	500	Ukn	Ukn	NAGS deficiency on mutation analysis	Corne et al. Mol Genet Metab 2011; 102;275.[34]
2	Screened at birth; female	Turkish First cousins	Yes; older sister died of severe hyperammonemia (NAGS deficiency not confirmed)	asymptomatic	No	393	Ukn, but 1961 on subsequent admission	Ukn	Second liver biopsy: reduced NAGS activity, later found to be homozygous for NAGS mutation	Gessler et al. Eur J Pediatr 2010;169:197–199.[35]
3	At birth; Ukn	Ukn	Ukn	coma, seizures	No	>1400	Ukn	Ukn	NAGS deficiency on mutation analysis	Nordenstrom et al. J Inherit Metab Dis 2007; 30:400.[36]
4	40 years; female	Ukn	Ukn	intermittent staring spells, nausea, recurrent vomiting, lethargy, ataxia, migraine headaches, eventually coma	No	500	Ukn	Ukn	NAGS deficiency on mutation analysis	Tuchman et al. Pediatr Res 2008;64(2):213-217.[22]
5	33 years; female	Ukn	Ukn	episodic altered mental status with coma after caesarean section. Psychomotor seizures	No	138 - 4781		Ukn	NAGS deficiency on mutation analysis	Grody et al. J Inherit Metab Dis.1994;17(5):566-574.[37] Caldovic et al.Human Mutat.2007;28(8)754-759.[3]
6	4 days; female	Ukn Yes; same village	Ukn	hypotonia, drowsiness, tremor, and no suck	No	182	1150	13	NAGS deficiency on mutation analysis	Guffon et al. J Pediatr 2005;147:260-262.[38] Schmidt et al. Biochim Biophys Acta. 2005;1740:54-59.[39]
7	3 months; male	French Yes; first cousins	Ukn	muscular axial hypotonia, hyporeactivity, hepatomegaly	No	113-367	841	19	NAGS deficiency on mutation analysis	Guffon et al. J Pediatr 2005;147:260-262.[38] Schmidt et al. Biochim Biophys Acta. 2005;1740:54-59.[39]
8	Screened at birth; male	Ukn No	Older sister died of severe hyperammonemia, no diagnosis made	asymptomatic	No	208	1114	<4	NAGS deficiency on mutation analysis	Guffon et al. J Pediatr 2005;147:260-262. Schmidt et al. Biochim Biophys Acta. 2005;1740:54-59.[39]
9	4 weeks; female	Ukn	No	recurrent vomiting, irritability, lethargy, later-on headaches, hallucinations	No	256	elevated	normal	Initially NAGS not assayed on liver biopsy Later NAGS deficiency on mutation analysis	Caldovic et al. J Pediatr 2004;145:552-554.[18]
10	9 years; female		Yes; younger sister case 9	lethargy, anorexia, vomiting, respiratory distress and seizures	No	978	1710	ND		
11	33 years; male	White No	None	post-operative combativeness, confusion, seizures	Yes	621	elevated	Low	NAGS deficiency on mutation analysis	Caldovic et al. Hum Mutat. 2005;25(3):293-298.[2]
12	12 years; male	Ukn No	Ukn	vomiting, decreased LOC with protein, EEG showed left temporal lobe spikes	No	350	801	21	Liver biopsy: L-Arginine unable to activate NAGS and normal CPS activity.	Belanger-Quintana et al. Eur J Pediatr. 2003;162(11)773.775.[40]
13	3 days; Ukn	Turkish Yes	Ukn	Ukn	Ukn	Ukn		Ukn	NAGS deficiency on mutation analysis	Haberle et al. Human Mutat.2003;21(6)593-597.[23] Heckmann et al. Acta Paediatr.2005;94(1):121-124.[41]
14	3-4 days; ukn	Turkish Yes	Ukn	Ukn	Ukn	Ukn		Ukn	NAGS deficiency on mutation analysis	Haberle et al. Human Mutat.2003;21(6)593-597.[23]
15	6 days; Ukn	German No	Ukn	Ukn	Ukn	Ukn		Ukn	Liver biopsy: No NAGS activity; later NAGS mutation found	Haberle et al. Human Mutat.2003;21(6)593-597.[23]
16	3 days; Ukn	Turkish Yes	Ukn	Ukn	Ukn	Ukn		Ukn	NAGS deficiency on mutation analysis	Haberle et al. Human Mutat.2003;21(6)593-597.[23] Schmidt et al. Biochim Biophys Acta. 2005;1740:54-59.[39]
17	3 days; female	German No	Ukn	signs of cerebral edema	Yes	942			Liver biopsy: reduced NAGS activity, NAGS mutation confirmed using cultured fibroblasts and DNA sequencing	Haberle et al. J Inherit Metab Dis 2003;26(6):601-605.[42] Haberle et al. Human Mutat.2003;21(6)593-597.[23]
18	16 hours; male	Faroe Islands Distant approximately 5 generations back	Ukn	tachypnea, jitteriness, hypertonia, hypothermia, coma	Yes	Ukn	elevated	ND	Post-mortem liver tissue: reduced NAGS Later parents found to be heterozygotes	Caldovic et al. Hum Genet 2003; 112:364–368.[43] Takanashi J., et al. Am J Neuroradiol (in press) 2002.[44]
19	3 days; female	Hispanic/ No	No	lethargy, anorexia, respiratory distress, coma, seizures	No	1700	1268	ND	Molecular studies: both homozygous for NAGS gene mutation	Caldovic et al. Hum Genet 2003; 112:364–368.[43]
20	2 days; female		Yes; younger sibling case 19	lethargy, anorexia, vomiting, respiratory distress and seizures	No	978	1710			
21	4 days; male	Iranian Jewish/ First cousins	Ukn One of twin (other twin unaffected)	unresponsive, seizures	No	1300	2652	ND	Initial liver biopsy inconclusive, later molecular analysis confirmed homozygous NAGS gene mutation	Elpeleg et al. Ann Neurol. 2002;52(6):845-89.[45]
22	at birth; male		Yes; younger brother to case 21	coma	No	1900	1732	ND	Homozygous NAGS gene mutation	
23	4 years; male	Ukn No	None	irritability, vomiting, lethargy, protein refusal, ataxia, worsened with VPA	No	229	920	Ukn	Liver biopsy: NAGS activity reduced 26% control	Forget et al. Acta Paediatr. 1999;88(12)1409-1411.[46]
24	12 years 11 months; female	Austrian/ Slovenian No	No	vomiting, protein aversion, restlessness, disorientation, aggression, hyperreflexia	No	221	1616	*12*	*Partial NAGS deficiency* Liver biopsy: NAGS activity reduced 15% control	Plecko et al. Eur J Pediatr. 1998;157(12):996-998.[47] Haberle et al. Hum Mutat. 2003;21(6):593-597.[23]

25	4 days; female	Ukn	vomiting, hyperventilation, respiratory alkalosis	No	316	1186	ND	Liver biopsy: NAGS activity <5% control	Morris et al J Inherit Metab Dis. 1998;21(8):867-868.[48]
26	20 years; male	First cousins Ukn Yes; first cousins	confusion, combative behaviour	No	525	1571	2	*Partial NAGS deficiency* Liver biopsy: NAGS activity <50% control	Hinnie et al. J Inherit Metab Dis. 1997;20(6):839-840.[49]
27	3-4 days; male	Ukn Yes; first cousins	oliguria, trembling, seizure, hypotonia, coma	No	530	1054	<1	Liver biopsy: NAGS activity <10% control	Guffon et al. J Inherit Metab Dis. 1995;18(1):61-65.[17]
28	5 years 7 months; male	Taiwanese No	history of lethargy and poor appetite	No	>200	850	24	Liver biopsy: NAGS activity reduced to 9.7% of control	Vockley et al. Biochem Med Metab Biol. 1992;47(1):38-46.[50]
29	5 months; female	Ukn No	vomiting, hypotonia, visual impairment, persistent head and body shaking	No	285	755	6	*Partial NAGS deficiency* Liver biopsy: NAGS activity reduced to 40% of control	Burlina et al. J Inherit Metab Dis. 1992;15(3):395-398.[51]
30	5-6 weeks; male	Ukn	Petit mal seizures in mat. aunt and mat. grandfather, migraine headaches in mother. Brother died at 14 months after developing seizures and liver failure	No	215	Elevated	Low	Liver biopsy revealed NAGS activity undetectable	Pandya et al. J Inherit Metab Dis. 1991;14(5):685-690.[52]
31	26 days; male	Yes (younger sibling case 30)	diarrhoea, irritability, tachypnea, hypertonia	No	185	Elevated	Low	None; positive family history	
32	13 months; female	Muslim First cousins	Yes, sister and male cousin (similar course)	Yes	241	549	ND	*Partial NAGS deficiency* Liver biopsy: NAGS activity reduced to 33% of control	Elpeleg et al. Eur J Pediatr. 1990 Jun;149(9):634-636.[53]
33	6 days; male	Ukn No	None	Yes	711	940	ND	Liver biopsy: NAGS activity Not detectable	Bachmann et al. J Inherit Metab Dis. 1988;11(2):191-193.[54]
34	Screened at 3 days; male	Ukn No	2 siblings died during neonatal period, postmortem analysis from 2nd sibling suggested ↑ ammonia	Died at age 9	242	1020	Ukn	Liver biopsy: NAGS activity Not detectable	Bachmann et al. N Engl J Med. 1981 Feb 26;304(9):543.[20] (INDEX CASE) Schubiger et al. Eur J Pediatr. 1991 Mar;150(5):353-356.[55]
35	38; male	Irish-Scottish No	None	No	434	1062	15	NAGS deficiency on mutation analysis	

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

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 neuroradiologists and deemed normal. Plasma ammonia was found to be markedly elevated at 434 umol/L (15-55 umol/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 umol/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[24]. 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 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.

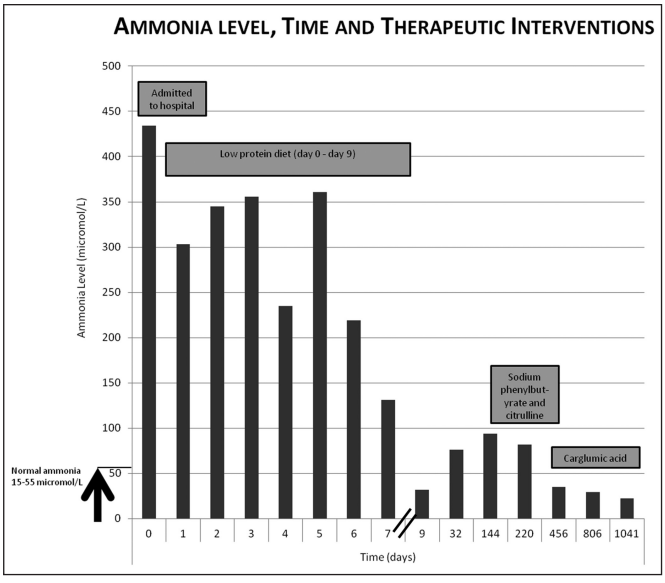

Figure 5: *Graph of our patient's ammonia level versus time with therapeutic interventions included. Day 0 is day of presentation. Normal ammonia values 15-55 umol/L.*

Conclusions

Plasma ammonia should be measured in all patients with an unexplained encephalopathy including cyclical presentations to identify potential underlying metabolic disorders. Electro-encephalogram can be a clue with the presence of triphasic waves indicating a metabolic encephalopathy. Hyper-ammonemia 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.

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