Published in final edited form as:

Mol Genet Metab. 2011 ; 104(1-2): 107–111. doi:10.1016/j.ymgme.2011.06.025.

Arginase I deficiency: Severe Infantile Presentation with hyperammonemia: more common than reported?

Shailly Jain-Ghai^{a,b}, Sandesh C. Sreenath Nagamani^c, Susan Blaser^{a,b}, Komudi Siriwardena^{a,b}, and Annette Feigenbaum^{a,b}

^aHospital for Sick Children 555 University Ave Toronto, Ontario, Canada M5G1X8

^bUniversity of Toronto Toronto, Ontario, Canada

^cBaylor College of Medicine One Baylor Plaza, Rm 814 Houston, Texas, USA 77030

Abstract

Enzyme defects of the urea cycle typically present with significant hyperammonemia and its associated toxicity, in the first few months of life. However, arginase I (ARG1) deficiency, a rare autosomal recessive disorder, has classically been the exception. ARG1 deficiency usually presents later in life with spasticity, seizures, failure to thrive and developmental regression. Neonatal and early infantile presentation of ARG1 deficiency with severe hyperammonemia remains rare and only six such cases have been described. We report a severely affected infant with ARG1 deficiency who presented at 6 weeks of age with lethargy, poor feeding and severe encephalopathy caused by hyperammonemia. The clinical and biochemical features of the proband and six other previously reported cases with neonatal or infantile-onset presentation of ARG1 deficiency with hyperammonemia are reviewed. In addition, the clinical spectrum of seven previously unpublished patients with later onset ARG1 deficiency, who also experienced recurrent hyperammonemia, is presented.

Several biochemical abnormalities have been postulated to play a role in the pathogenesis of the neurological changes in ARG1 deficiency including hyperargininemia, elevated guanidino compounds and elevated glutamine levels, as well as the hyperammonemia. The index case demonstrated many of these. The cases reviewed here suggest a genotype/phenotype correlation and advocate for the addition of arginine as a primary target in newborn screening programs.

Keywords

Arginase deficiency; hyperammonemia; hyperargininemia; orotic acid; guanidino compounds

© 2011 Elsevier Inc. All rights reserved

Corresponding Author: Dr. Annette Feigenbaum Address: The Hospital for Sick Children, 555 University Ave, Toronto Ontario M5G1X8 Canada Phone: 416 813 5340 annette.feigenbaum@sickkids.ca/asjfeigenbaum@gmail.com.

Contact Information:

Dr. Shailly Jain Ghai (please note that the family name is Jain Ghai) shailly.jain@sickkids.ca

Dr. Sandesh CS Nagamani nagamani@bcm.edu

Dr. Susan Blaser susan.blaser@sickkids.ca

Dr. Komudi Siriwardena komudi.siriwardena@sickkids.ca

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

The urea cycle consists of six sequential enzymatic steps that convert nitrogen derived from protein to urea. The first three enzymes of the cycle, N-acetyl glutamate synthase, carbamoyl phosphate synthase, and ornithine transcarbamylase function in the mitochondria while the latter three, argininosuccinate synthase, argininosuccinate lyase and, arginase I function in the cytoplasm [1]. Deficiency of any of these enzymes can lead to significant elevation of ammonia. Hyperammonemia with symptoms of brain injury in the first days to months of life is the classic presentation of most of the urea cycle enzyme deficiencies. Arginase I (ARG1) deficiency, a rare autosomal recessive disorder of ureagenesis has classically been the phenotypic exception within urea cycle disorders. Patients with ARG1 deficiency typically present later in life with spasticity, seizures and failure to thrive [1].

Arginase exists in two isoforms, ARG1, which is expressed in the liver, erythrocytes and salivary glands [2] and arginase II (ARG2), which is found predominantly in the renal tissues [3]. It is believed that the comparatively mild presentation of ARG1 deficiency may be the result of over expression of ARG2 [3]. The activity of ARG2 may not be protective in the nervous system and thus the spasticity and developmental delay progress, although at a slower pace [3]. Deficiency of ARG1 leads to accumulation of arginine which is a precursor for synthesis of nitric oxide [4] and guanidino compounds [5], both of which may play a role in the pathogenicity of this condition. Treatment of ARG1 deficiency with dietary protein restriction has been beneficial in slowing the progression of symptoms or completely eradicating them if started before symptom onset [6]. However, adherence to this strict diet is difficult and does not control arginine levels completely.

Neonatal presentation of ARG1 deficiency with significant hyperammonemia is rare and only six case reports exist in the literature [7, 8, 9, 10, 11, 12]. In this report, we present an additional infant with ARG1 deficiency with hyperammonemia and compare the clinical and biochemical features of the proband and review the existing literature.

2. Case Presentation

a. Index Case

The index case was a male born at term to a first cousin consanguineous couple of Iraqi descent. There were two healthy siblings. There were no problems until six weeks of age when he presented with a 12 hour history of poor feeding progressing to irritability, lethargy, respiratory distress and seizures, requiring intubation and ventilation. Initial venous plasma ammonia was 537 $\mu\text{mol/L}$ and a repeat level two hours later was 739 $\mu\text{mol/L}$. With continuous veno-venous hemodialysis (CVVHD) and IV sodium phenylacetate/sodium benzoate (Ammonul®), the ammonia level normalized within ten hours of admission. The plasma amino acid analysis results became available as the IV arginine solution was being prepared, thus the patient did not receive IV arginine. Glutamine was 1398 $\mu\text{mol/L}$ (normal, 1–746), arginine 841 $\mu\text{mol/L}$ (normal, 53–71) citrulline 34 $\mu\text{mol/L}$ (normal, 0–26), ornithine 23 $\mu\text{mol/L}$ (normal, 37–61) with urine orotic acid of 228.9 mmol/mol creatinine (normal, 1 – 3.2). MRI brain scan performed 24 hours after presentation revealed diffuse and abnormally increased signal intensity of the deep and central white matter (Figure 1). A follow-up MRI brain one week later, showed evolution of signal change in white matter tracts, some of which suggested pre-Wallerian degeneration.

The patient recovered well from the initial insult and regained oral feeding. Oral sodium phenylbutyrate was titrated up to a dose of 330 mg/kg/day , but he continued over the next year and half to have recurrent hyperammonemic episodes. At 19 months of age, the weight and height were at the 75th centile and head circumference was at 3–10th centile (previously

at the 50th centile at 3 months of age). Neuropsychological assessment at 19 months chronological age showed non-verbal and motor development to be equivalent to 15 months and verbal development equivalent to 11 months developmental age. He continued to have generalized axial and limb hypertonia with hyperreflexia, although he started to ambulate with support at 15 months.

Dietary management has included protein restriction which varied from 1.8 – 2.2 g/kg/day including essential amino acids (Cyclinex formula) of 1.1 – 1.4 g/kg/day, but arginine remained elevated at >200 μ mol/L. He remained seizure free on low dose phenobarbital. Molecular analysis found a previously reported nonsense homozygous mutation in *ARG1*, c. 61C>T (p.R21X) in exon 2. In view of the orotic aciduria, the ornithine transcarbamylase gene was sequenced and was normal.

Figure 2 compares the levels of glutamine, arginine and ammonia over the first 18 months of life. There seems to be a parallel relationship between glutamine and arginine as the levels are often elevated concurrently. This relationship was not observed between elevations in ammonia and glutamine and only an inconsistent correlation with hyperargininemia and hyperammonemia was observed. More data and further analysis is needed. Figure 3 graphs the levels of plasma ornithine and urine orotic acid, over the first 18 months of life. This figure suggests that low ornithine levels correspond to higher orotic acid values.

b. Previously unpublished Arginase I deficiency cases with hyperammonemia

Table 1 describes the data of seven previously unpublished cases from 5 families of *ARG1* deficiency who presented later in life. The majority of these patients had recurrent hyperammonemic crises (6/7), even when the onset was later in life. Of note, 5 of these cases also experienced seizures and all, as expected, show spastic diplegia and developmental delay.

3. Discussion

We present a case of *ARG1* deficiency that presented in early infancy with hyperammonemia. Only six such cases have been described in the literature (Table 2). These cases demonstrate the wide variation in neonatal presentation of *ARG1* deficiency. *ARG1* deficiency is commonly recognized as a later onset condition with a consistent presentation of spastic diplegia and seizures, but consistency is not seen in the neonatal presentation, which continues to remain rare. Liver dysfunction has been reported in other cases of *ARG1* deficiency but severe liver disease (liver failure, cirrhosis) is rare [8, 13]. We did not document liver dysfunction in any of the previously unpublished cases described here.

The current algorithm for the management of hyperammonemia includes arginine bolus and/or infusion [14] which is needed in most of the other UCDs. We suggest that in view of the *ARG1* cases with hyperammonemia, albeit rare, the specific diagnosis is made even more urgently and if possible, before intravenous arginine therapy is initiated, to avoid any added insult.

The genotypes of the cases summarized here suggest that cases with neonatal presentation of *ARG1* deficiency may have severe mutations, as noted by the presence of nonsense, splice site or frameshift mutations while the classic later onset *ARG1* deficiency patients have at least one missense mutation (Table 1 and 2). Not all patients have been genotyped, and further studies are needed to further delineate any genotype-phenotype correlation.

As indicated in the introduction, the activity of *ARG2* as well as alternate pathways for excretion of nitrogen rich intermediates may also play a role with pathogenesis and severity

of disease. The neurological changes observed in typical ARG1 deficiency, without hyperammonemia, may be due to a significant increase in CSF arginine or CSF guanidino compounds [5, 7, 10, 15, 16]. Guanidino compounds are neurotoxic and can lead to seizures and demyelination [12, 17]. Our patient had elevations in creatine (2548 mmol/mol creatinine, 28–1700), α -N-acetylarginine (15.4 mmol/mol creatinine, 2–11.3), argininic acid (9.2 mmol/mol creatinine, 0.4–3.4), and γ -guanidinobutyric acid (17.1 mmol/mol creatinine, 1.7–7.9) (courtesy of Dr. Andreas Schulze). The guanidino compounds and arginine metabolites may lead to oxidative damage to the brain [1, 13] and need to be further investigated in ARG1 deficiency [16]. Hyperammonemia in some cases also contributes to the CNS toxicity as discussed in the literature [18, 19].

Neuroimaging features in typical hyperargininemia have been rarely reported and imaging features may be non-specific or even absent. Mild cerebral and cerebellar atrophy in two siblings with signal change in the posterior putamina and insular cortex [20], corticospinal tract alterations on DTI [21] have been previously described. Two of the neonatal presentation cases discussed here had global brain edema [7, 10]. A case of later onset ARG1 deficiency, included in our series as case 7 (Table 1), had a normal brain MRI at age 14, although DTI was not available at time of imaging. Changes including ischemic changes of the depth of sulcus on T2 and diffusion weighted images, initial global or focal edema, basal ganglia involvement followed by myelin delay, ulegyria, and cystic lesions are recognised in most other UCDs in which hyperammonemia is a factor [22]. A case report of ARG1 deficiency with neonatal onset and hyperammonemia at 4 years of age revealed an end-stage brain with significant atrophy, cystic leukoencephalopathy with increased signal in the bilateral basal ganglia, thalami and hippocampal atrophy [12]. Our patient, who did have hyperammonemia, presented with findings at least as severe as those described in the other UCD disorders presenting with acute hyperammonemic crises in infancy.

An intriguing biochemical abnormality noted in ARG1 deficiency is orotic aciduria [23; 25] and it was present in the proband and other cases reviewed here. Naylor *et al* [24] proposed two mechanisms for orotic aciduria in ARG1 deficiency; first, a functional decrease in OTC activity as a result of low ornithine due to deficiency of ARG1, and the second, as a 'back-up' phenomenon due to accumulation of distal substrates affecting OTC activity. As a result, accumulated carbamoyl phosphate would be shunted towards the pyrimidine biosynthetic pathway leading to orotic aciduria [24]. Figure 3 indicates an inverse relationship between plasma ornithine and urine orotic acid in the proband, supporting the first hypothesis. Thus, we suggest ornithine supplementation may be considered as a treatment modality in certain patients.

Another interesting observation made in our patient was the dramatic reduction in arginine post red blood cell transfusion, given as priming for the CVVHD. The decrease in arginine lasted for approximately six weeks, the expected half-life of the transfused cells (Figure 2). ARG1, unlike other urea cycle enzymes, is present in erythrocytes and in ARG1 deficiency, the RBC arginase is also decreased [26]. Upon transfusion, the arginine levels may decline due to presumed activity of transfused ARG1 [26]. While this decrease in arginine is well studied in context of immunosuppression post transfusion [26], it has not been discussed in the treatment of ARG1 deficiency. We suggest this may need further study especially as hyperargininemia may play a critical role in the pathogenesis of the neurological insult. Repeated transfusions would have complications long term, but could be considered during severe exacerbations or illness.

Recurrent hyperammonemic episodes are not commonly described in ARG1 deficiency, although in the cases presented here such episodes were not infrequent (Table 1). In addition, Prasad *et al* [17] described two siblings with late diagnosis ARG1 deficiency. Both

had recurrent hyperammonemic crises which proved fatal in the brother with the milder presentation many years after diagnosis. Thus, vigilance and avoidance of precipitating factors for hyperammonemic crises is required even in ARG1 deficiency. Treatment with low protein diet aimed at lowering arginine in ARG1 deficiency is generally felt to be the most effective management and many patients show improvement or stabilization of the neurological symptoms [6, 13]. Cases where treatment has been initiated from birth have demonstrated good clinical outcomes [6]. Untreated patients show slow progression of symptoms, failure to thrive and spasticity [13]. Although dietary management may be therapeutic, better modalities to normalise arginine levels, the suspected culprit in causing the neurological symptoms, is needed in ARG1 deficiency. Liver transplantation is another option and has been reported in two patients with ARG1 deficiency, both with good results although it may not reverse the initial brain injury [27, 28]. Life-long treatment with diet may still be needed to keep arginine levels low. The combination of newborn screening and in selected patients, liver transplantation may offer a better outlook for ARG1 deficiency.

Our region does not use arginine as a target metabolite on newborn screening. Retrospective analysis of the newborn bloodspots of our patient showed significantly elevated arginine (365 $\mu\text{mol/L}$; Normal <100). In the case presented by Picker *et al* [7], arginine was also elevated on NBS. Thus, it is possible in some cases to detect hyperargininemia on NBS, leading to early initiation of treatment and reduction in the neurological sequelae of this otherwise very difficult to treat condition. We suggest that arginine be added as a target metabolite in all newborn screening programs where this is not the case.

4. Conclusion

In this paper we emphasize that neonatal presentation of ARG 1 deficiency with hyperammonemia, although rare, should always be considered. Recurrent hyperammonemia may be more of a risk factor than previously considered in this condition, even in the late onset cases, and may contribute to significant brain injury.

Acknowledgments

The authors acknowledge the clinical research staff at the Hospital for Sick Children (Emily Bailey; Ashley Orton) and Dr Andreas Schulze for useful discussion and the guanidino analyses. This work was supported in part by the Rotenberg Family Fund (Sickkids Foundation) and the Urea Cycle Disorders Consortium (NIH Grant RR019453) a part of the Rare Disease Clinical Research Consortium (RDCRN) and the NIH Office of Rare Diseases Research (ORDR). The views expressed in written materials or publications do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

We acknowledge and appreciate the support of the families and colleagues in the Urea Cycle Diseases Consortium and the useful discussions on the metab-L forum.

6. References

- [1]. Crombez EA, Cederbaum SD. Hyperargininemia due to liver arginase deficiency. *Mol Genet Metab.* 2005; 84:243–251. [PubMed: 15694174]
- [2]. Yasuda, N.; Moriwaki, K.; Furuyama, S. Distribution and properties of arginase in the salivary glands of four species of laboratory mammals.
- [3]. Grody WW, Kern RM, Klein D, Dodson AE, Wissman PB, Barsky SH, Cederbaum SD. Arginase deficiency manifesting delayed clinical sequelae and induction of a kidney arginase isoenzyme. *Hum Genet.* 1993; 91:1–5. [PubMed: 8454280]
- [4]. Luiking YC, Engelen MPKJ, Deutz NEP. Regulation of nitric oxide production in health and disease. *Curr Opin Clin Nutr Metab Care.* 2010; 13:97–104. [PubMed: 19841582]

- [5]. De Deyn P, Marescau B, Lornoy W, Becaus I, Lowenthal A. Guanidino compounds in uraemic dialysed patients. *Clin Chim Acta*. 1986; 157:143–50. [PubMed: 3719996]
- [6]. Cederbaum SD, Yu H, Grody WW, Kern RM, Yoo P, Iyer RK. Arginases I and II: do their functions overlap? *Mol Genet Metab*. 2004; 81(Suppl 1):S38–44. [PubMed: 15050972]
- [7]. Picker JD, Puga AC, Levy HL, Marsden D, Shih VE, et al. Arginase deficiency with lethal neonatal expression: evidence for the glutamine hypothesis of cerebral edema. *J Pediatr*. 2003; 142(3):349–52. [PubMed: 12640389]
- [8]. Braga AC, Vilarinho L, Ferreira E, Rocha H. Hyperargininemia presenting as Persistent Neonatal Jaundice and Hepatic Cirrhosis. *J Peds Gastro Nutr*. 1997; 24:218–221.
- [9]. Jorda A, Rubio V, Portoles M, Vilas J, Garcia-Pino J. A new case of arginase deficiency in a Spanish male. *J Inher Metab Dis*. 1986; 9:393–397. [PubMed: 3104676]
- [10]. Scholl-Bürgi S, Baumgartner Sigl S, Häberle J, Haberlandt E, Rostásy K, Ertl C, Eichinger-Öttl U, Heinz-Erian P, Karall D. Amino acids in CSF and plasma in hyperammonaemic coma due to arginase I deficiency. *J Inher Metab Dis*. Dec 6.2008 Epub ahead of print.
- [11]. Schiff M, Benoist JF, Cardoso ML, Elmaleh-Berges M, Forey P, Santiago J, Ogier de Baulny H. Early onset hyperargininaemia: A severe disorder? *J Inher Metab Dis*. 2009; 165 online.
- [12]. Segawa Y, Matsufuji M, Itokazu N, Utsunomiya H, Watanabe Y, Yoshino M, Takashima S. A long-term survival case of arginase deficiency with severe multicystic white matter and compound mutations. *Brain and Development*. 2011; 33:45–48. [PubMed: 20456883]
- [13]. Scaglia F, Lee B. Clinical, Biochemical, and Molecular Spectrum of Hyperargininemia due to Arginase I deficiency. *Am J Med Genet Part C*. 2006; 142:113–120. [PubMed: 16602094]
- [14]. Häberle J. The management of hyperammonemia. *Eur J Pediatr*. 2011; 170:21–34. [PubMed: 21165747]
- [15]. Cederbaum SD, Shaw KN, Spector EB, Verity MA, Snodgrass PJ, Sugarman GI. Hyperargininemia with arginase deficiency. *Pediatr Res*. 1979; 13:827–33. [PubMed: 481955]
- [16]. Deignan JL, De Deyn PP, Cederbaum SD, Fuchshuber A, Roth B, Gsell W, Marescau B. Guanidino compound levels in blood, cerebrospinal fluid, and post-mortem brain material of patients with argininemia. *Mol Genet Metab*. 2010; 100(Suppl):S31–6. [PubMed: 20176499]
- [17]. Prasad AN, Breen JC, Ampola MG, Rosman P. Argininemia: A treatable genetic cause of progressive spastic diplegia simulating cerebral palsy: case reports and literature review. *Journal of Child Neurology*. 1997:301–309. [PubMed: 9378897]
- [18]. Norenberg MD, Martinez-Hernandez A. Fine structural localization of glutamine synthetase in astrocytes of rat brain. *Brain Res*. 1979; 161:303–10. [PubMed: 31966]
- [19]. Albrecht J, Dolińska M. Glutamine as a pathogenic factor in hepatic encephalopathy. *J Neurosci Res*. 2001; 65:1–5. [PubMed: 11433423]
- [20]. Gungor S, Akinci A, Firat AK, Tabel Y, Alkan A. Neuroimaging findings in hyperargininemia. *J Neuroimaging*. 2008; 4:457–62. [PubMed: 18321250]
- [21]. Oldham MS, VanMeter JW, Shattuck KF, Cederbaum SD, Gropman AL. Diffusion tensor imaging in arginase deficiency reveals damage to corticospinal tracts. *Pediatr Neurol*. 2010; 42:49–52. [PubMed: 20004862]
- [22]. Blaser S, Feigenbaum A. A neuroimaging approach to inborn errors of metabolism. *Neuroimag Clin N Am*. 2004; 14:307–329.
- [23]. Snyderman SE, Sansaricq C, Chen WJ, Norton PM, Pansalkar SV. Argininemia. *J Pediatr*. 1977; 90:563–568. [PubMed: 839367]
- [24]. Naylor EW, Cederbaum SD. Urinary pyrimidine excretion in Arginase deficiency. *J Inher Metab Dis*. 1981; 4:207–210. [PubMed: 6796772]
- [25]. Brosnan EM, Brosnan JT. Orotic Acid Excretion and Arginine Metabolism. *The Journal of Nutrition*. 2007; 137:1656S–1661S. [PubMed: 17513443]
- [26]. Bernard A, Meier C, Lopez N, May J, Chang P, Boulanger B, Kearney P. Packed red blood cell-associated arginine depletion is mediated by Arginase. *J trauma*. 2007; 63:1108–1112. [PubMed: 17993958]
- [27]. Leonard JV, McKiernan PJ. The role of liver transplantation in urea cycle disorders. *Mol Genet Metab*. 2004; 81(Suppl 1):S74–8. [PubMed: 15050978]

- [28]. Santos Silva E, Martins E, Cardoso ML, Barbot C, Vilarinho L, Medina M. Liver transplantation in a case of argininaemia. *J Inherit Metab Dis*. 2001; 24:885–7. [PubMed: 11916327]

Figure 1.

MRI brain of index case at 24 hours post presentation. a) T2W image demonstrates diffuse abnormally increased signal intensity of the deep and central white matter. b) MRS (TE 35) demonstrates marked increase in the GLX/GLU peaks as indicated by the arrow c) DWI and d) ADC maps show extensive involvement of the deep white matter tracts and the juxtacortical white matter in the depths of the sulci. ADC confirms diffusion restriction.

Figure 2.
Proband's glutamine, arginine and ammonia levels over the first 18 month of life.

Figure 3.
Proband's plasma ornithine and urine orotic acid levels. X and Y axis are not to scale.
Numbers in small boxes refer to level of urine orotic acid. The break in the Orotic acid line (=) implies unavailable data for urine orotic acid from 4 to 14 months of life.

Table 1

	Case 1 (M)	Case 2* (F)	Case 3* (F)	Case 4* (F)	Case 5 (F)	Case 6 (F)	Case 7 (F)
	Unknown, First note at 20 Y	3Y, Diagnosed at 11 Y	8Y	5Y	unknown (now 39Y)	11Y	5Y
Development	LD	LD	LD	DD	Severe Delay	LD	LD
Spastic Diplegia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Seizures	Refractory	Controlled	yes	Yes	No	No	Yes
	Recurrent	Mild but recurrent	Recurrent	Recurrent	None	Recurrent	Two since presentation
	n/a	c.700G>C (p.D234H) homozygous	c.700G>C (p.D234H) homozygous	c.700G>C (p.D234H) homozygous	C.61C>T (P.R21X), C.892C>G (p.A289P)	c.466–1G>C, homozygous	c.292G>A (P.G98S), c.560+5G>A

LD: male; n/a: not available

Mol Genet Metab. Author manuscript; available in PMC 2012 September 1.

Table 2

	Proband	Segawa <i>et al</i> 11	Schiff <i>et al</i> 10	Scholl-Burgi <i>et al</i> 9	Pickler <i>et al</i> 6	Braga <i>et al</i> 7	Jorda <i>et al</i> 8
	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14
Sex	Male	Female	Female	Male	Female	Female	Male
Age at presentation	6 weeks	18 days	3 weeks	36 days	3 days	2 months	5 days
Clinical presentation	Poor feeding, lethargy, cerebral edema, seizures	vomiting, lethargy, then seizures and hypertension	Resp distress, seizures, lethargy, coagulopathy	vomiting, poor feeding, lethargy, seizures, infection	poor feeding, cerebral edema, seizures	jaundice, vomiting, hepatomegaly, splenomegaly	jaundice, hepatomegaly, vomiting, seizures, lethargy, hand tremor
Spasticity	yes	yes	no	no	yes	no	yes
Ammonia (presentation) in umol/L	739	563 (done at age 4 yrs for the first time)	250	>400	114	142	198
Arginine at presentation (normal 11–65) in umol/L	841	341–1049	680	971	881	1756	170
Orotic Acid	elevated (see Fig 3)	“elevated”	“elevated”	“elevated”	n/a	“elevated”	“elevated”
Dialysis	Yes	No	No	Yes	No	No	Yes
Other		CSF Glutamine normal		CSF Glutamine elevated	CSF Glutamine elevated	Hepatic cirrhosis and cholestasis	
Initial Outcome	Partial recovery	Partial recovery	Partial recovery	Full recovery	Deceased 5 days	Full recovery	Deceased 7 wks
Follow-up (months)	19 months	32 years	12 months	21 months		26 months	
Well	Yes	Yes	Yes	Yes		Yes	
Developmental Delay	Mild	Severe	Severe	No		No	
Spasticity	No, hyper-reflexia	Yes	Yes	No		No	
Seizures	Yes (controlled)	Yes	n.a	No		No	
Failure to thrive	W>75%, OFC3–10%	n.a	No, microcephaly	All parameters at 3%		All parameters below 3%	
Subsequent Hyperammonemic Episodes	Multiple	No	No	No		No	
NBS Arginine level	Elevated	n.a	n.a	n.a.	Elevated	n.a	n.a
Genetics (mutations)	homozygous C.612C>T (R21X)	c.262del4bp	homozygous IVS4-2A>G	c.647_648ins32 exon 6.	n.a	n.a	n.a
		c.77del1bp		C.871OT (p.Arg291X)			
RBC arginase activity	n.a.	<1%	1%	n.a.	1%	0.50%	2%

n.a.: not available

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript