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Magnetic resonance imaging findings and neurodevelopmental outcomes in neonates with urea-cycle defects

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Abstract: The urea-cycle functions to facilitate ammonia excretion, a disruption of which results in the accumulation of toxic metabolites. The neurological outcome of neonatal-onset urea-cycle defects (UCDs) is poor, and there are no good predictors of prognosis beyond ammonia levels at presentation. The role of neuroimaging in the prognosis of neonatal-onset UCDs is unclear. We describe the magnetic resonance imaging (MRI) findings of two patients with neonatal-onset UCDs (argininosuccinic aciduria and citrullinemia) at presentation and at 2-year follow-up, and present a review of the literature on neuroimaging in this age-group. We observed two potentially significant distinct patterns of cerebral involvement on MRI: (1) a central and focal pattern of involvement limited to the basal ganglia, perirolandic regions, and internal capsule; and (2) diffuse involvement of the cerebral cortex, internal capsule, basal ganglia, and variably thalami and brain stem. Patients with more diffuse findings tended to have higher serum glutamine peaks and worse neurological outcomes, while those with central involvement, aggressive acute management, and early liver transplantation tended to have better outcomes. We propose that MRI imaging of the brain may have prognostic value following presentation with neonatal UCDs, particularly in identifying patients at risk for poor outcome. The role and timing of follow-up neuroimaging is currently unclear. Further collaborative studies are necessary to evaluate whether patterns of MRI findings vary with specific UCD subtypes, and are predictive of clinical outcomes in neonatal UCDs.

Keywords: hyperammonemia, amino acid metabolism, inborn error, metabolism, inborn errors, infant, newborn, magnetic resonance imaging

Introduction

Urea-cycle defects (UCDs) result in hyperammonemia and the accumulation of glutamine and various toxic metabolites. Neonatal-onset UCDs are associated with poor neurodevelopmental outcome, often resulting in cerebral palsy and developmental delay.[1–3] Left untreated, these disorders result in progressive seizures, coma, and death. The use of magnetic resonance imaging (MRI) is increasingly reported in neonatal hyperammonemia;[4–7] however, the association with neurological outcome is unclear.

We present two cases of neonatal-onset UCD, their brain MRI findings, and neurodevelopmental outcome at 2 years. We reviewed the literature and summarize the reported patterns of MRI findings in this population, and hypothesize their significance in relation to subtypes of UCD, biochemical markers, and neurodevelopmental outcome.

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Case 1: argininosuccinic aciduria

A full-term female infant presented on her second day of life (DOL) with seizures, hypovolemic shock, multi-organ system dysfunction, peak serum ammonia in the acute phase

of 1,092 μmol/L (normal <80 μmol/L), and peak glutamine in the acute phase of 1,728 μmol/L (normal 376–709 μmol/L, Table 1). Ammonia-lowering agents (sodium benzoate, sodium phenylacetate, and L-arginine) were promptly initiated; she had approximately 12 hours of hemodialysis. Her ammonia normalized within 36 hours. Quantitative plasma amino acid analysis confirmed a diagnosis of the UCD, argininosuccinic aciduria (argininosuccinic acid 853 μmol/L, citrulline 292 μmol/L [normal 10–24 μmol/L], urine argininosuccinic acid 58,617 μmol/L). At 20 months, she was noted to have moderate language and motor delays (Table 2).

MRI was performed on DOL 8 (Figure 1A and B). T1- and T2-weighted images showed increased signal intensity of the globus pallidus, caudate nucleus, internal capsule, and bifrontal corona radiata, extending into the perirolandic regions. There was no restricted diffusion. Follow-up imaging at 25 months (Table 3) revealed residual signal change of the caudate nucleus and globus pallidus, with globus pallidus volume loss (Figure 1C).

Case 2: citrullinemia

This full-term female infant presented on DOL 7 with seizures, peak serum ammonia of 1,345 μmol/L, and peak serum glutamine of 3,055 μmol/L (Table 1). Ammonia-lowering agents were initiated; she had 4 hours of hemodialysis. Her ammonia level normalized within 24 hours. The quantitative amino acid profile yielded a diagnosis of citrullinemia (citrulline 4,074 μmol/L, ornithine 25 μmol/L [normal 48–211 μmol/L], arginine 62 μmol/L [normal 6–140 μmol/L], no urine argininosuccinic acid). At 27 months, she displayed mild motor and language delays, microcephaly and failure to thrive (less than third percentile for head circumference, height, and weight; Table 2).

MRI on DOL 11 (Figure 2A and B) demonstrated diffuse restricted diffusion with predominance posteriorly, sparing the superior frontal lobe and parts of the temporal lobe. There was involvement of the globus pallidus, internal capsule, corpus callosum, thalami, and cerebral peduncles. At 24 months of age, repeat MRI (Table 3) showed increased signal of the periventricular white matter with associated posterior white-matter volume loss and ventricular enlargement (Figure 2C).

Discussion

Patterns of brain MRI findings and urea-cycle defects

A review of the literature found four case reports of brain MRIs of eight neonates after acute presentation with neonatal-onset hyperammonemia, summarized in Table 1.[4–7] Based on these cases, we interpreted two patterns of cerebral

Table 1 Location of cerebral involvement, as indicated by magnetic resonance imaging (MRI), of cases of neonatal-onset urea-cycle defects in the subacute phase of recovery after presentation, as well as timing of presentation and MRI, peak serum ammonia, and glutamine levels

	Diagnosis	Age at diagnosis	Age at MRI	Peak ammonia* (μmol/L)	Peak glutamine* (μmol/L)	Pattern of cerebral involvement	Perirolandic	Insula
Patient 1	ASA	DOL 2	DOL 8	1,092	1,728	Central	+	
Patient 2	Citrullinemia	DOL 7	DOL 11	1,345	3,055	Diffuse	+	
Patient 3[4]	CPS I	DOL 2	2 weeks	978	1,710	Central	+	+
Patient 4[4]	OTCD	DOL 4	2 weeks	1,420		Central	+	+
Patient 5[4]	CPS I	DOL 2	2 weeks	1,700	1,268	Central	+	+
Patient 6[5]	Citrullinemia	DOL 5	DOL 8	2,083	3,067	Diffuse	+	+
Patient 7[7]	OTCD	DOL 2	DOL 12	952	6,491	Diffuse	+	
Patient 8[6]	OTCD	DOL 2	DOL 5	3,035	2,883	Diffuse	+	+
Patient 9[6]	OTCD	DOL 1	DOL 8	2,652	3,308	Diffuse	+	+
Patient 10[6]	Citrullinemia	DOL 2	DOL 8	2,196	3,809	Diffuse	+	+
Patient 11[6]	OTCD	DOL 1**	DOL 5	2,684	3,398	Central		+

Notes: *Peak concentration during initial acute presentation; **recognized within 8 hours and corrected rapidly in 24 hours (patients 1, 2, and 3 recognized belatedly). Patient 1 and 2 are Case 1 and 2 of this study, respectively.

Abbreviations: ASA, argininosuccinic aciduria; CPS I, carbamoyl phosphate synthetase I deficiency; CN, caudate nucleus; GB, globus pallidus; OTCD, ornithine transcarbamylase deficiency; DOL, day of life; MOD, multiorgan dysfunction; N/A, not applicable.

involvement on MRI: diffuse and central/focal. The "diffuse" pattern consists of extensive involvement of the cerebral cortex (particularly the posterior cortices excluding the superior frontal and medial temporal lobes), basal ganglia, and in some cases, thalami and brain stem; the "central" pattern consists of signal changes limited to the basal ganglia, perirolandic region, and internal capsule.

The diffuse pattern of cerebral involvement was more commonly associated with high peak serum glutamine levels (>2,800 μmol/L) than serum ammonia levels during the acute phase of presentation. In addition, we note that the diffuse pattern of cerebral involvement was common to cases of citrullinemia. While our patient with argininosuccinic aciduria presented with multiorgan dysfunction, which may have contributed to the pattern of cerebral involvement noted on MRI, the pattern of involvement was similar to other patients with UCD who did not present with multiorgan dysfunction. There was insufficient information provided in the literature to demonstrate a relationship between duration of hyperammonemia and patterns of cerebral involvement.

Neuropathophysiology of urea-cycle defects and findings on neuroimaging

Authors have described a correlation between severity of outcome and duration and/or peak concentration of ammonia.[8] Current hypotheses suggest the direct effect of hyperammonemia on the brain causes more injury than cerebral edema from its osmotically active toxic metabolite, glutamine, alone.[8] In order to detoxify ammonia, glutamine synthetase (GS) catalyzes the condensation of ammonia and glutamate to form glutamine in astrocytes.[8,9] However, if the GS-enzyme pathway becomes saturated, ammonia will accumulate. Elevated cerebral ammonia has a number of neurophysiological effects, including increased cerebral edema from impaired glucose oxidation and subsequent lactate accumulation,[10] loss of cerebral autoregulation,[10] effects on neurotransmitters, synaptic transmission, nitric oxide synthesis,[9,11] and stimulation of *N*-methyl-D-aspartate receptors, which may downregulate GS.[9] In our study, the demonstrated association between more diffuse cerebral involvement and high glutamine peaks builds upon the findings of Bireley et al,[6] and seems contrary to what is understood about the pathogenesis of hyperammonemia.

The bulk of the literature dedicated to understanding the neuropathogenesis of UCDs focuses on the neurotoxic effects of glutamine and hyperammonemia. However, there may be additional neurotoxic effects of specific metabolites of different subtypes of UCD, such as with arginase deficiency[3] and citrullinemia.[12] This may contribute to the diffuse pattern of

Basal ganglia	Internal capsule	Temporal	Parietal–occipital	Frontal	Thalami	Corpus callosum	Brain stem	Restricted areas in diffusion-weighted imaging	
+ (GB&CN)	+							None	MODs
+ (GB&CN)	+		+	+	+	+	+	Diffuse, sparing superior frontal and parts of temporal lobes	No MODs
+ (GB)								Unknown	No MODs
+ (GB)								Unknown	No MODs
+ (GB&CN)								Unknown	No MODs
+ (GB)	+	+	+		+			Diffuse, corresponds with T2 signal changes	No MODs
+	+	+	+	+		+	+	Diffuse, as described, including optic radiata, cerebral peduncle, scattered through cortex (particularly posterior)	No MODs
+			+/–	+			+	Diffuse, as described	
+		+	+	+	+		+	Diffuse, as described	
+		+	+/–	+	+		+	Diffuse, as described	
+								Limited, as described	

Table 2 Neurodevelopmental and long-term outcome of patients with a diffuse or central pattern of cerebral involvement, as well as peak serum ammonia and glutamine levels after acute presentation by subtype of urea-cycle defect

	Diagnosis	Peak ammonia* (μmol/L)	Peak glutamine* (μmol/L)	Pattern of cerebral involvement (acute phase)	Further episodes of hyperammonemia prior to follow-up
Patient 1	ASA	1,092	1,728	Localized	Yes**
Patient 2	Citrullinemia	1,345	3,055	Diffuse	No
Patient 3[4]	CPS 1	978	1,710	Localized	Yes
Patient 4[4]	OTCD	1,420		Localized	Unknown
Patient 5[4]	CPS 1	1,700	1,268	Localized	Unknown
Patient 6[5]	Citrullinemia	2,083	3,067	Diffuse	No
Patient 7[7]	OTCD	952	6,491	Diffuse	Unknown
Patient 8[6]	OTCD	3,035	2,883	Diffuse	Unknown
Patient 9[6]	OTCD	2,652	3,308	Diffuse	N/A
Patient 10[6]	Citrullinemia	2,196	3,809	Diffuse	N/A
Patient 11[6]	OTCD	2,684	3,398	Localized	No

Notes: *Peak concentration during initial acute presentation; **two severe episodes at 18 and 26 months old, respectively, and 1 minor episode at 28 months old; ***where applicable. Patient 1 and 2 are Case 1 and 2 of this study, respectively.
Abbreviations: ASA, argininosuccinic aciduria; CPS I, carbamoyl phosphate synthetase I deficiency; DOL, day of life; OTCD, ornithine transcarbamylase deficiency; WOLS, withdrawal of life support.

cerebral involvement noted in all patients in this series with a diagnosis of citrullinemia.

Neuroimaging and neurodevelopmental outcome

The neurodevelopmental outcomes of patients were graded according to the schema introduced by Bireley et al[6] (Table 2). Patients with mild outcomes had transient symptomatology during periods of hyperammonemia that completely resolved. Those with moderate outcomes had persistent neurocognitive delays or neurological abnormalities. Patients with severe outcomes had profound neurocognitive delays or severe spastic quadriplegia. Generally, patients with more extensive cortical involvement had more severe neurodevelopmental outcomes (Table 2). An exception was our citrullinemia case (patient 2). In contrast, children with central cerebral involvement had variable neurodevelopmental outcomes. The subtype of UCD was not predictive of neurodevelopmental outcome.

That more extensive cerebral involvement noted on MRI translates into more severe neurodevelopmental outcome follows. However, the fact that not all patients with diffuse involvement had severe outcomes (ie, patient 2), and that patients with a central pattern of cerebral involvement or similar subtypes of UCD had variable outcomes, reflects the complexity of the neuropathophysiology of these disorders. Important contributing factors may include cumulative patient-specific factors, such as the duration of hyperammonemia on presentation, chronic exposure to mild hyperammonemia, number of subsequent episodes of severe hyperammonemia (patient 2 had no subsequent episodes), and exposure to other toxic UCD metabolites.

Early and aggressive management of patients with neonatal-onset UCD, regardless of subtype, may modify the neurocognitive outcome. The patients with better neurological outcomes (patients 4[4] and 11[6]), had liver transplants at an early age, early and aggressive management (patient 4[4]), or no repeated episodes of hyperammonemia (patients 2 and 11[6]). The patients with more severe neurodevelopmental outcomes (patients 3[4] and 5[4]) had repeated episodes of hyperammonemia and/or transplantation at a later age.

Patients with brain-stem and thalamic involvement tended to have worse neurodevelopmental outcomes, with the exception of patient 2. While Bireley et al[6] hypothesized that thalamic injury may be partially caused by secondary anoxic insult from hemodynamic instability, it may simply represent more severe cerebral disease (our patient with thalamic involvement remained hemodynamically stable). In contrast to Bireley et al's[6] findings, restricted diffusion was not consistently associated with worse outcome.

Pattern of cerebral involvement demonstrated in follow-up imaging

The degree of signal resolution and development of cerebral volume loss demonstrated by follow-up MRIs

Neurodevelopmental sequelae	Neurodevelopmental outcome	Age at death***	Cause of death***	Age at liver transplant***
Moderate	Moderate language and motor delay			
Moderate	Microcephaly, failure to thrive, mild language and motor delay			
Severe	Truncal hypotonia, appendicular hypertonia, choreoathetosis, global neurodevelopmental delay			8 months
Moderate	Nonoral food intake, age-appropriate development			6 weeks
Moderate	Moderate neurodevelopmental delays			7 months
Severe	4 months old: microcephaly, severe neurodevelopmental delay, hypotonia, head lag, hyperreflexia			
Severe	DOL 89: microcephaly, no head control, suck and swallow uncontrolled, hyperreflexia, clonus bilaterally			
Severe	"Severe quadriparetic cerebral palsy with minimal development"	15 months	Unknown	
Severe	"Neurological devastation"	DOL 15	WOLS	
Severe	"Severely depressed neurological function"	DOL 20	WOLS	
Moderate	Hypotonia and mild motor delays at 1 year old			11 weeks

varied (Table 3). The consistent findings of signal changes and volume loss in the basal ganglia and posterior cerebral cortex (including parieto-occipital encephalomalacia in severe cases) reinforce the importance of these structures in the pathogenesis of this disease.

From the information presented, it is difficult to demonstrate a clear relationship between the pattern of cerebral involvement noted on MRI after acute presentation and long-term follow-up. This is due to the variability in the timing and indication of follow-up imaging in this series, as well as the small number of patients with each subtype of UCD who underwent later imaging. In addition, it is unclear to what extent the pattern of cerebral involvement seen in later imaging reflects subsequent episodes of hyperammonemia. For example, the later imaging of patient 8 was the only follow-up imaging that demonstrated restricted diffusion. However, this MRI was done 2 days after the patient presented with an episode of hyperammonemia, and thus likely reflects this acute process. Overall, we question the clinical utility of follow-up imaging, as it may not change clinical management when there are no further episodes of hyperammonemia.

Limitations of this review include the small sample size, which reflects the rarity of this disease, and lack of access to full case images and developmental assessments from the literature. In addition, for each case, the number of days that an MRI was done after acute presentation varied from 3 days to 2 weeks, which may affect the degree of diffusivity noted on the respective diffusion-weighted imaging.[13,14]

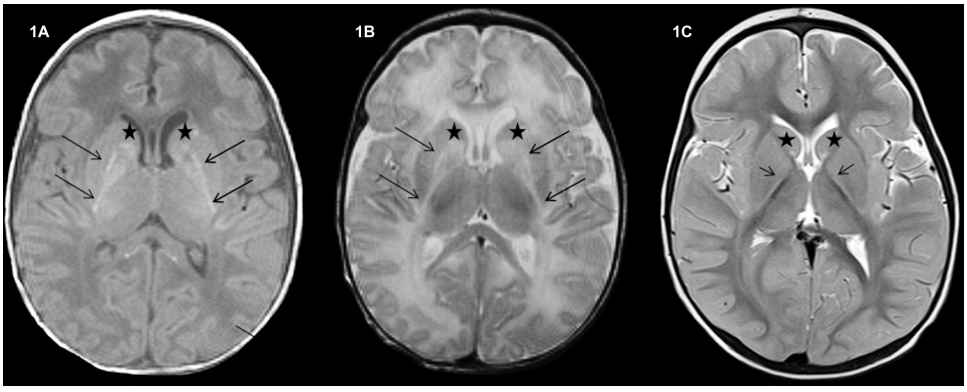

Figure 1 Axial T1- (**A**) and T2-weighted magnetic resonance images (**B**) of case 1 show increased signal intensity of the internal capsule, globus pallidus (arrows) and caudate nucleus (stars), bifrontal corona radiata, extending into the perirolandic regions (not shown). Axial T2-weighted magnetic resonance image (**C**) of case 1 done at follow-up at 25 months reveals residual signal change of the caudate nucleus (stars) and globus pallidus, with decreased size of the globus pallidus (arrows).

Table 3 Location of cerebral involvement demonstrated by follow-up magnetic resonance imaging (MRI) by subtype of urea-cycle defect, age, and imaging indication, also including number of subsequent episodes of hyperammonemia between presentation and follow-up imaging

	Diagnosis	Further episodes of hyperammonemia prior to follow-up	Indication for follow-up MRI	Age at follow-up MRI	Volume loss	Basal ganglia	Thalami	Parietooccipital leukomalacia	Other
Patient 1	ASA	Yes*	Routine follow-up	25 months	GP only	T2 increased signal GP and CN			
Patient 2	Citrullinemia	No	Routine follow-up	24 months	Diffuse posterior	T2 increased signal GP and CN	T2 increased signal	Insula	
Patient 3[4]	CPS I	Yes	After 2 significant episodes of hyperammonemia	7 months	Diffuse atrophy; VL mostly BG	T2 prolongation GP and CN; T1 shortening of putamen			Slightly delayed myelination
Patient 6[5]	Citrullinemia	No	Unknown	4 months	Extensive				Subcortical cysts (especially occipital); ulegyric changes
Patient 7[7]	OTCD	Unknown	Unknown	3 months	Global			Bilateral	T1 high signal cerebral white matter
Patient 8[6]	OTCD	Yes	2 days after hyperammonemic episode	11 months	Moderate		Restricted diffusion		Restricted diffusion temporal and occipital
Patient 11[6]	OTCD	No	Unknown	6 months	Moderate				Resolution of previously restricted diffusion

Notes: *Peak concentration during initial acute presentation; **recognized within 8 hours and corrected rapidly in 24 hours (patients 1, 2, and 3 recognized belatedly); Patient 1 and 2 are Case 1 and 2 of this study, respectively.
Abbreviations: ASA, argininosuccinic aciduria; BG, basal ganglia; CPS I, carbamoyl phosphate synthetase I deficiency; CN, caudate nucleus; DOL, day of life; GP, globus pallidus ; OTCD, ornithine transcarbamylase deficiency; VL, volume loss.

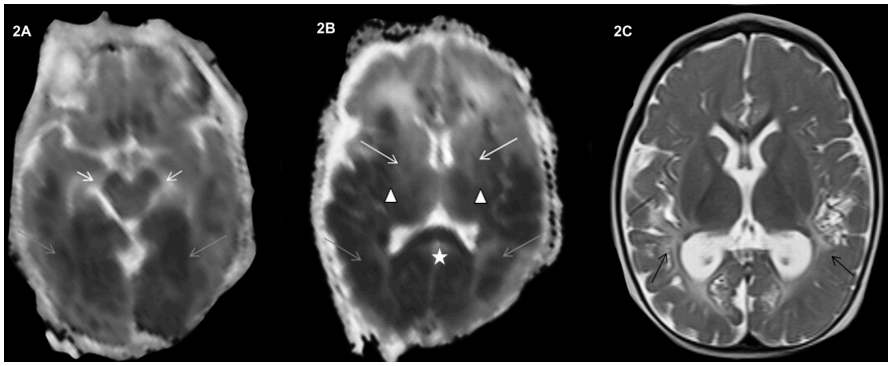

Figure 2 Axial apparent diffusion coefficient (**A** and **B**) magnetic resonance images of case 2 show diffuse restricted diffusion with predominance posteriorly (arrow), sparing the superior frontal lobe and parts of the temporal lobe. There was involvement of the globus pallidus, internal capsule, cerebral peduncles (short arrows), corpus callosum (star), and thalami (triangles). Axial T2-weighed magnetic resonance image (**C**) of case 2 at 24 months of age shows increased signal of the periventricular white matter (arrows) with associated posterior white-matter volume loss and enlargement of the ventricular system.

Conclusion

For clinicians involved in the acute management of neonates presenting with UCDs, prognostication is extremely important, as some parents will elect to withdraw life-sustaining therapy if the projected neurodevelopmental outcome is devastating. We hypothesize that the pattern of cerebral involvement seen in the subacute phase of recovery from hyperammonemia on MRI, as well as early biomarkers such as glutamine, may have a role in predicting neurodevelopmental outcome in these children. If MRI reveals a central pattern of involvement, strict and aggressive management and early hepatic transplantation may help preserve neurological function. However, given the rarity of this disease, scarcity of published case reports, and inconsistency in neurodevelopmental reporting and follow-up presented in the literature, clinical decision-making based on neuroimaging results alone should be done with caution. Large clinical trials are necessary to delineate more clearly the predictive value of neuroimaging after acute presentation, as well as the relative importance of aggressive therapeutics, in the long-term neurodevelopmental outcome of these children. The clinical utility of follow-up imaging is unclear.

Disclosure

The authors have no financial or personal relations that may provide a conflict of interest.

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