

Metabolic and Neuropsychological Phenotype in Women Heterozygous for Ornithine Transcarbamylase Deficiency

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We compared neurocognitive indices with clinical status, mutation analysis, and urea synthetic capacity in 19 women heterozygous for ornithine transcarbamylase deficiency. Although as a group, these women had average IQ scores, they displayed a specific neuropsychological phenotype with significant strengths in verbal intelligence, verbal learning, verbal memory, and reading, and significant weaknesses in fine motor dexterity/speed and nonsignificant weaknesses in non-verbal intelligence, visual memory, attention/executive skills, and math. This suggests selective vulnerability of white matter and better preservation of gray matter. When the group was divided into symptomatic and asymptomatic subgroups, based on either clinical history or residual urea synthetic capacity, the asymptomatic subgroup outperformed the symptomatic subgroup on all tested domains of neuropsychological functioning. Furthermore, the amount of residual urea synthetic capacity was predictive of several end point cognitive measures. There was no correlation between neonatal versus late-onset mutation or between normal or abnormal allopurinol challenge and neuropsychological outcome. In sum, we identified a specific metabolic and neurocognitive phenotype in women heterozygous for ornithine transcarbamylase deficiency. The findings support the importance of maintaining meticulous metabolic control in children with urea cycle disorders, because even mildly symptomatic subjects demonstrate cognitive deficits.

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Inherited urea cycle disorders represent one of the most common group of inborn errors of metabolism, with an overall incidence of approximately 1 in 8,200.^{1,2} Disorders involving deficiencies of each of the five urea cycle enzymes as well as three related cofactors and transporters have been described.³ The most common of these disorders is ornithine transcarbamylase deficiency (OTCD). It also is the only disorder inherited as an X-linked trait, and it has an estimated incidence of 1 in 14,000.^{2,4} Approximately 60% of OTCD hemizygous male subjects have a mutation that is present around the active site of the enzyme; these infants present with hyperammonemic coma in the newborn period. The rest have mutations in the periphery and develop symptoms that are less severe and later in onset.⁵ In neonatal-onset disease, the mortality rate is high, and the majority of survivors sustain severe brain injury resulting in mental retardation, cerebral palsy, and seizure disorders.⁶ In male subjects with partial de-

ficiencies, outcome is better but mortality and morbidity rates remain high.⁷

In heterozygous OTCD female subjects, there is a broad spectrum of symptomatology. Approximately 85% are asymptomatic; the remainder has symptoms ranging from behavioral and learning disabilities to protein intolerance, cyclical vomiting, and episodes of hyperammonemic coma.^{8–10} Symptomatic women usually have a “neonatal-onset” mutation,⁵ and they presumably develop hyperammonemia because of skewed lyonization. Based on this experience, one would predict, and we have, in fact, found, a wide range of residual urea synthetic capacity and associated clinical symptoms and cognitive deficits in OTCD heterozygous women.^{5,11,12}

To better understand hyperammonemic-induced cognitive and behavior alterations, we performed in this study comprehensive neuropsychological testing of 19 mildly symptomatic and asymptomatic high-

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functioning women who were heterozygous for OTCD. We hypothesized that (1) there would be a specific neuropsychological phenotype; (2) the symptomatic heterozygotes would be at a cognitive disadvantage compared with asymptomatic carriers; and (3) the difference could be predicted by the amount of residual urea synthetic capacity and by the mutation type.

Subjects and Methods

Subject Recruitment and Data Selection

This study was the outgrowth of a phase I adenoviral gene therapy safety trial for OTCD, the protocol for which has been published previously.¹³ All prospective subjects had a family history taken and studies were performed to assure a correct diagnosis of OTCD: DNA analysis to detect a specific OTC mutation⁵ and allopurinol challenge¹⁴ and ¹⁵N stable isotope studies to determine residual urea synthetic capacity¹¹ (Table 1). Clinically stable symptomatic and asymptomatic

OTCD heterozygous women were entered into the study. Twenty-two women participated in the screening process for the portion of the study reported in this article; two were eliminated from consideration because of unrelated neurological disorders, and one because the diagnosis of OTCD was uncertain. The 19 remaining women all agreed to undergo the neuropsychological testing. The control group for the biochemical studies (stable isotope, allopurinol challenge) comprised eight women who did not have OTCD and were unrelated to the study subjects. The control group for the neuropsychological studies was the reported standardization samples for the individual tests used.

Definition of Symptomatic/Asymptomatic Ornithine Transcarbamylase Deficiency Heterozygote

The definition of *symptomatic* versus *asymptomatic* in the OTCD heterozygotes was based both on biochemical and clinical criteria. The biochemical criterion was the degree of impairment of urea synthetic capacity based on (1) the stable

Table 1. Demographics, Family History, and Clinical Symptoms

Age (yr)	Symptomatic/Asymptomatic	Family History (proband)	Clinical Symptoms	¹⁵ N incorporation (mmol/4 hr)	Peak Orotate (μmol/mol creatinine)	OTC Mutation	Education (yr)
31	S	Neonatal-onset affected brother	Lethargy (coma x1), OTC activity in liver 23% of normal	18.67	76.0	g→ a substitution at splice site of intron 9/exon 10 ^a	16
21	S	Neonatal-onset affected brothers	Lethargy, vomit (3 episodes)	1.35	49.7	None found	12
27	A	Neonatal-onset affected brothers	None	59.15	1.5	None found	16
38	S	Neonatal-onset maternal male cousins	Hyperammonemic episode, OTC activity 25% in liver	38.89	121.4	None found	12
27	A	Affected sister, neonatal-onset affected son	None	41	Not done	None found	14
24	S	Affected daughter	Protein intolerance	17.1	Not done	Exon 5, Leu 139Ser ^a	13
50	S	Late-onset affected son	None	44.4	7.0	Exon 8, Arg 277 Trp ^b	13
45	A	Late-onset affected son	Protein intolerance	30.03	9.9	Exon 9, Leu304Phe ^b	14
21	S	Neonatal-onset affected son	Protein intolerance, migraine	Not done	Not done	Exon 6, Asp 196 Val ^a	10
42	A	Late-onset affected son	None	37.61	Not done	None done	16
39	A	Neonatal-onset affected son	Cyclical vomiting, protein intolerance	26.19	677	Exon 5, Arg 141 Ter ^a	13
27	A	Neonatal-onset affected son	None	55.19	11.6	None found	16
44	S	Late-onset affected son	Lethargy, confusion 2x per year	28.52	720	None found	13
45	A	Neonatal-onset affected son	None	39.83	435.3	Exon 1, Arg 23 Ter ^a	15
25	A	Late-onset affected son	None	27.5	17	Exon 8, Arg277Trp ^b	12+
51	S	Neonatal-onset affected son	Episode of coma	29.7	91.7	Exon 9, Arg 320 Leu ^a	16+
36	A	Late-onset affected son	None	34.05	85	Exon 3, Thr 93 Ala ^b	12+
42	A	Late-onset affected son	None	34.5	318.5	Exon 5, Ser132Phe ^b	16+
53	A	Late-onset affected sons	None	24.16	114.6	None found	13+

^aNeonatal onset.

^bLate onset.

OTC = ornithine transcarbamylase.

isotope incorporation of (¹⁵N) into urea, and (2) orotate excretion following an allopurinol challenge.^{11,14} For the ¹⁵N study, we analyzed the results using 1 standard deviation (SD) below the mean as the definition of *symptomatic*; this is compatible with the clinical observation that approximately 15% of women heterozygous for OTCD are symptomatic.^{9,15} For the allopurinol challenge, a much less sensitive measure, we used 4 SD above the control mean to define symptomatic. The clinical definition of *symptomatic* relied on clinical history and responses to a structured interview obtained by one of us (J.W.) who was blinded to the results of the biochemical studies. Subjects who had documented hyperammonemic episodes or the presence of protein intolerance, including symptoms of headaches and/or altered conscious state, were designated as *symptomatic*.

Stable Isotope Studies

Stable isotope studies were performed in the morning, after an overnight fast. ¹⁵N-NH₄Cl (20mg/kg; 1,400mg maximum) was given orally in water. Heparinized venous blood was sampled at 0, 30, 60, 90, 120, 180, and 240 minutes after administration of the isotope. Incorporation rate of ¹⁵N-NH₃ into urea was determined as previously described.¹¹ The data are expressed as the cumulative formation of ¹⁵N-urea after the oral administration of ¹⁵N-NH₄Cl (1.4gm; 99 atom percentage of excess).

Allopurinol Challenge Test

The allopurinol challenge test has been used as a diagnostic test for OTCD heterozygosity.¹⁴ This provides a second measure of impairment of urea synthetic activity. Following the protocol of Hauser and colleagues,¹⁴ we gave subjects a 300mg allopurinol tablet at the same time that the stable isotope study was performed, and urine was collected in 6-hour aliquots for a 24-hour period to measure orotic acid excretion. The peak orotate excretion was used as the marker.

Mutation Analysis

Mutations in the OTC gene were identified either by single-strand conformational polymorphism screening followed by direct sequencing or by direct sequencing of the 10 exons and exon-intron borders using peripheral blood.¹⁶ For characterizations of small deletions, respective polymerase chain reaction fragments were cloned into a plasmid, and several colonies then were sequenced. The deleterious nature of a mutation was determined for some mutations by expression studies and for others by several criteria including structural and catalytic modeling,¹⁷ sequence conservation among known OTC enzymes in various species,¹⁸ and sequence analysis on hundreds of control sequences.⁵

Neuropsychological Tests

Global IQ was measured by the Full Scale IQ on the Wechsler Adult Intelligence Scale-Third Edition. To reduce problems associated with multiple comparisons, we assigned individual scores on the neuropsychological tests to 1 of 10 domains of functioning based on conventional clinical practice (Table 2): standardized scores (*Z*-scores) were derived based on standardization norms available for each test. The

direction of the *Z*-scores was always the same, with positive scores indicating better performance and negative scores indicating worse performance in comparison with the standardization sample. We had complete data sets for all the cognitive measures in 15 subjects (ie, 25% missing data). This reduced our ability to analyze the following domains: nonverbal learning (21% missing data) and attention/executive (26% missing data).

Statistical Analysis

Demographic characteristics of the patients were described as means and frequencies. Functional urea synthetic capacity (¹⁵N outcomes) and allopurinol challenge test results (orotic acid excretion) were described by ranges and means. The reliability of using each of the laboratory measures for diagnosis compared with using clinical symptoms was assessed by kappa coefficient. Because of the small sample size, and the fact that most of the neuropsychological results were not normally distributed, nonparametric statistical tests were utilized. Hence, for hypothesis testing medians and ranges were reported instead of means. To test the hypothesis that the performance on neuropsychological domains was different in the OTCD patients than the standardization sample, we used the Wilcoxon signed rank test on the normalized scores of each neuropsychological measure to zero. To test the hypothesis that the scores for the neuropsychological domains were different comparing *symptomatic* to *asymptomatic* OTCD pa-

Table 2. Domains of Neuropsychological Functioning: Individual Scores on the Tests Were Assigned to 1 of 10 Domains of Functioning

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- *Verbal intelligence* was measured by the Verbal Comprehension Index of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)
 - *Verbal learning* was measured by the total scores for Logical Memory I and the Word Lists I of the Wechsler Memory Scale-Third Edition (WMS-III)
 - *Verbal memory* was measured by the total scores for Logical Memory II and Word Lists II of the WMS-III.
 - *Nonverbal intelligence* was measured by the Perceptual Organization Index of the WAIS-III, total score on the Judgment of Line Orientation Test, and score for the Copy Trial of the Rey Complex Figure Test and Recognition Trial (RCFTT).
 - *Nonverbal learning* was measured by the scores for Faces I of the WMS-III and Immediate Recall Trial of the RCFTT.
 - *Nonverbal memory* was measured by the scores for Faces II of the WMS-III and Delayed Recall Trial of the RCFTT.
 - *Fine motor* was measured by combining the scores for the dominant and nondominant hands on the Grooved Pegboard. A global score was used because the motor findings were not lateralizing for most subjects.
 - *Attention/executive* functioning was measured by the Working Memory Index of the WAIS-III, Trail B score of the Trail Making Test, the Color Word score on the Stroop Color and Word Test, and the sum total of five items on the Wisconsin Card Sorting Test.
 - *Reading and math* were measured by the Wide Range Achievement Test-3 (WRAT-3).
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tients, the Mann–Whitney tests were applied. Finally, Spearman correlation coefficients were obtained to examine the correlation of ^{15}N , allopurinol, and mutation with neuropsychological domains. To obtain improved sensitivity for this exploratory clinical study, we set the criterion of statistical significance at p value 0.1. This allows a higher risk of type I error. However, efforts were made to decrease the problems associated with multiple comparisons by (1) grouping the 39 neuropsychological test scores into 10 domains as outcomes, and (2) treating ^{15}N as the primary predictor, whereas the other medical indices were treated as references only. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

Results

Demographics, Family History, and Clinical Symptoms

The subjects in this study were 19 white women whose ages ranged from 21 to 53 years (mean, 35.6 ± 10.5 years; see Table 1). Among these individuals, only 1 (5%) did not finish high school; 13 (68%) had a college or higher education. This represents a high achieving group, because nationwide only 23% of women have a Bachelor's degree (US Census 2002). Each had a family history of a proband with OTCD. Ten women had clinical symptoms that qualified them as having *symptomatic* OTCD; four had episodes of hyperammonemia/coma, and six had protein intolerance without documented hyperammonemic episodes.

Mutation Type Did Not Predict Stable Isotope/Allopurinol Challenge Results

Mutation analysis was performed in 18 of 19 subjects. In seven subjects, no mutation was detected. Four had mutations associated with late-onset disease, and seven had mutations associated with neonatal-onset disease (according to the findings of Tuchman and colleagues¹⁹). In each case, the identified mutation was consistent with the proband's age at presentation of symptoms (see Table 1).

We analyzed the differences in results of stable isotope studies and of the allopurinol challenge as a function of whether the subject had a neonatal- or late-onset mutation. This analysis was limited to the 11 subjects who had relevant mutation information. The median ^{15}N ammonium incorporation for subjects with the neonatal-onset mutation was 34.1mmol/L/min versus 26.2 for late-onset mutation ($p = 0.07$). The median peak orotate excretion after an allopurinol challenge was $263.5\mu\text{mol/mmol creatinine}$ for neonatal-onset mutation and 17.0 for late-onset mutation ($p = 0.11$). The correlation was 0.52 ($p = 0.12$) between the ^{15}N ammonium incorporation and mutation type, and -0.61 ($p = 0.08$) between orotate and mutation type.

Stable Isotope Studies Predict Clinical Symptomatology, whereas Allopurinol Challenge Does Not

Stable isotope studies were performed in 18 of the 19 subjects and in 8 controls. The mean ^{15}N -ammonium incorporation rate into ^{15}N -urea was 43.9mmol/L/min (range, 26.6 – 59.7) in the control group and 32.7 (range, 1.35 – 59.2) in the study population. Using a cutoff at 33.9 (ie, 1 SD below the control mean), we found that seven of the nine subjects who were identified as *symptomatic* based on clinical history were also identified as symptomatic by the ^{15}N study. There were two false-positives comparing ^{15}N ammonium incorporation to clinical symptoms in the *asymptomatic* group. This ^{15}N ammonium incorporation cutoff provides a κ of 0.56 , with a 95% confidence interval of 0.17 to 0.94 . The sensitivity was 77.8% and specificity 77.8% .

Fifteen subjects and eight controls underwent an allopurinol challenge. Mean peak orotate level after allopurinol administration in controls was $3.7\mu\text{mol/mmol creatinine}$ (range, 1.3 – 11.9). These results were similar to those reported by other investigators.^{14,20} In the study population, mean peak orotate was $182\mu\text{mol/mmol creatinine}$, with a range of 1.5 to 720 . Using 4 SD above the mean as the cutoff for an abnormal allopurinol challenge, we considered levels above 20 to fall in the *symptomatic* group. Of the 10 patients who had diagnoses of being positive by clinical symptoms, 3 did not have allopurinol challenges performed. Among the seven who did, six (86%) were positive. With clinical symptoms as the gold standard, the specificity of the allopurinol challenge test is 50% and the sensitivity is 86% . The positive predictive value is 60% , and negative predictive value is 80% . The κ coefficient was 0.34 , with a 95% confidence interval of 0.08 to 0.78 . This indicates that in contrast with the significant agreement between the ^{15}N and clinical symptoms, the agreement between allopurinol challenge and clinical symptoms was not significant. Thus, the allopurinol challenge was not a sensitive enough measure to be helpful in this analysis.

Ornithine Transcarbamylase Deficiency Heterozygotes Have a Specific Neuropsychological Phenotype

Our group of adult OTCD heterozygotes had full-scale IQ scores that fell in the average range (mean IQ, 101). The previously reported pattern of verbal IQ greater than performance IQ¹² was in the expected direction but did not reach statistical significance. In the context of average IQ, the group demonstrated a specific phenotype or neurobehavioral profile (see Table 3). Compared with the standardization sample, the OTCD group as a whole performed significantly better in the following domains: verbal memory ($p = 0.004$), verbal learning ($p = 0.013$), reading ($p = 0.035$), and

verbal intelligence ($p = 0.064$). In contrast, the group performed significantly lower than the normative population in fine motor ($p = 0.019$). Weaknesses were also evident for nonverbal memory, attention/executive, nonverbal learning and math, but these domains did not reach statistical significance.

Asymptomatic Carriers Outperform Symptomatic Heterozygotes Defined by Clinical History on All Neuropsychological Domains

The sample then was divided into *symptomatic* or *asymptomatic* groups based on clinical history obtained by interview. Table 4 compares the performance of both groups on all the domains. Both groups again showed a similar neuropsychological phenotype (ie, higher scores for verbal memory, verbal learning, verbal intelligence in comparison to nonverbal learning, nonverbal memory, math, fine motor). The asymptomatic group, however, outperformed the symptomatic group on all the domains of functioning. This difference was statistically significant for verbal learning ($p = 0.009$), verbal memory ($p = 0.014$), verbal intelligence ($p = 0.019$), nonverbal intelligence ($p = 0.037$), and nonverbal memory ($p = 0.094$). Thus, the asymptomatic group showed better preservation of strengths and less marked deficits.

Asymptomatic Carriers Outperform Symptomatic Heterozygotes Based on ^{15}N Ammonium Incorporation Results on All Neuropsychological Domains

A similar comparison was performed comparing the performance of symptomatic versus asymptomatic based on ^{15}N ammonium incorporation results. Table 4 compares the performance of both groups on all the domains. The asymptomatic group outperformed the symptomatic group on all the domains of functioning. This difference was statistically significant for atten-

tion/executive ($p = 0.033$), nonverbal intelligence ($p \leq 0.052$), reading ($p = 0.056$), math ($p = 0.077$), and fine motor ($p = 0.093$). Thus, the asymptomatic group again showed better preservation of strengths and less marked deficits.

There was a correlation between stable isotope studies, but not allopurinol challenge or mutation type, and neuropsychological domains.

There was a significant positive correlation between individual ^{15}N ammonium incorporation and individual performance in math ($p = 0.0013$), attention/executive ($p = 0.002$), and reading ($p = 0.032$). There was no correlation with the other neuropsychological domains. Thus, the degree of deficit in urea synthetic capacity was not predictive of most of the neuropsychological domains. It was, however, a good predictor for both the most sensitive neurocognitive measure (ie, attention/executive functions) and academic outcome.

Neuropsychological outcome was not significantly associated with symptomatic/asymptomatic status based on allopurinol test. Using a combination of the stable isotope study, the allopurinol challenge and clinical symptoms did not significantly change the results when compared with using the clinical symptoms alone or the stable isotope study alone.

Finally, neuropsychological outcome was not significantly associated with neonatal versus late-onset mutation or whether the proband had neonatal versus late-onset disease (see Table 4).

Discussion

In this study, we were interested in elucidating the relationship between gene, biochemical markers, brain, and behavior in one inborn error of metabolism, OTCD. Although it is a rare condition, we felt that the methodology would be applicable to more common disorders as well as providing important information about the need for treatment in this group of patients.

Table 3. Summary of Neuropsychological Results (Z-scores)

Neuropsychological Domain	N	Mean	SD	Median	Range		p (signed rank test)
					Min	Max	
Verbal memory ^a	19	1.31	0.33	1.33	-1.00	4.00	0.004
Verbal intelligence ^a	19	0.81	0.48	1.06	-2.48	4.72	0.064
Verbal learning ^a	19	0.95	0.36	0.67	-1.66	4.00	0.013
Reading ^a	19	0.29	0.12	0.33	-1.00	1.07	0.035
Nonverbal intelligence	19	0.09	0.42	0.13	-3.20	2.80	0.815
Nonverbal learning	15	-0.57	0.61	-0.10	-4.00	3.27	1.000
Math	19	-0.29	0.23	-0.13	-2.13	1.60	0.359
Nonverbal memory	19	-1.28	0.47	-1.20	-5.00	2.60	0.167
Fine motor ^a	19	-1.93	0.55	-1.48	-8.28	0.73	0.019
Attention/Executive	14	-1.87	1.45	-1.11	-15.73	4.82	0.791

^aStatistically significant.

SD = standard deviation.

Table 4. Median Neuropsychological Domains by Clinical Symptom, ¹⁵N, and Mutation

Neuropsychological Domain	Symptomatic		Asymptomatic		<i>p</i> ^a	¹⁵ N < 33.9 mmol/L/min		¹⁵ N > 33.9 mmol/L/min		<i>p</i> ^a	No Late-Onset Mutation		Late-Onset Mutation		<i>p</i> ^a
	n	Median	n	Median		n	Median	n	Median		n	Median	n	Median	
Verbal intelligence	10	-0.29	9	1.13	0.019	9	0.42	9	1.09	0.331	6	0.76	5	2.19	0.400
Nonverbal intelligence	10	-1.13	9	1.20	0.037	9	-0.60	9	1.27	0.052	6	-1.23	5	1.20	0.400
Reading	10	0.00	9	0.60	0.175	9	0.00	9	0.60	0.056	6	0.53	5	0.33	0.750
Math	10	-0.77	9	0.20	0.153	9	-0.60	9	0.20	0.077	6	-0.60	5	-0.13	0.750
Verbal learning	10	0.17	9	2.33	0.009	9	0.34	9	1.34	0.250	6	0.34	5	1.34	0.390
Nonverbal learning	7	-0.50	8	0.65	0.271	7	-0.10	7	1.00	0.443	5	-0.10	5	0.30	0.540
Verbal memory	10	0.50	9	2.00	0.014	9	0.67	9	2.00	0.267	6	1.00	5	1.33	0.780
Nonverbal memory	10	-2.27	9	0.40	0.094	9	-1.20	9	-0.43	0.401	6	-1.45	5	0.67	0.400
Attention/executive functioning	6	-3.23	8	0.95	0.220	6	-4.10	8	1.39	0.033	3	-4.32	5	0.74	0.490
Fine motor	10	-1.95	9	-0.74	0.347	9	-2.76	9	-0.74	0.093	6	-1.19	5	-0.30	0.400

^a*p* value of two sample Mann–Whitney tests.

It is clear that conditions causing hyperammonemia lead to cognitive impairment, however, it has been difficult to differentiate the effects of this metabolic alteration from ancillary abnormalities, for example, the effects of liver failure in hepatic encephalopathy.²¹ Even in children with inborn errors of the urea cycle, in which hyperammonemia is not associated with marked liver dysfunction, it has been difficult to separate the effects of nitrogen accumulation from those of hypoxia-ischemia and increased intracranial pressure that accompany hyperammonemic coma.²² Survivors of neonatal hyperammonemic coma resulting from urea cycle disorders generally have mental retardation²³; and neuropathology of children who have died shows cavitated changes in the cortex with few residual neurons and marked gliosis.^{24,25}

To study cognitive deficits resulting directly from long-term but modest nitrogen (ammonium) accumulation, without major secondary insults, we chose to evaluate women with partial OTCD. These heterozygotes are an ideal group to study because they present with a broad range of symptomatology but are generally neurologically intact. Prior studies (eg, Batshaw and colleagues¹²) established that even the asymptomatic OTCD heterozygotes are at a cognitive disadvantage compared with their unaffected sisters. However, that study used limited psychometric testing, which relied primarily on global cognitive indices that are not particularly helpful in specific neurobehavioral attributes of a clinical group.

In our study, we used a comprehensive but focused battery to look for specific neuropsychological markers, and we found a specific neuropsychological phenotype. What is most compelling about these findings is that this group of fairly highly educated women (ie, 95% high school graduates; 68% with college education) with grossly intact intellectual functioning showed departures from the normative sample that were fairly consistent. This group significantly outperformed the

normative sample in verbal intelligence, verbal learning, verbal memory, and reading. In contrast, they scored significantly lower than the normative sample for nonverbal memory and fine motor functions. In addition, the group scored lower, albeit not at a significant level, for math and attention and executive functions. Scores for nonverbal intelligence and nonverbal learning, while not lower than the normative sample, represented relative weaknesses for this group.

This particular neurobehavioral profile or phenotype is consistent with a nonverbal learning disability (NLD). Subjects with NLD often exhibit specific neuropsychological assets (eg, language, rote memory, language arts) that are considered gray matter correlates and deficits (eg, visual-spatial, tactile, and motor deficits that often are accompanied by attention/executive weaknesses) that are typically associated with disturbances in white matter. Another reported clinical feature of NLD is the higher risk of psychiatric disorders, particularly in adulthood. Thirteen of our subjects completed the MMPI-2, but we did not find any evidence of significant personality disturbance.

Although the particulars of the NLD syndrome have evolved over time.^{26–28} Rourke's most recent interpretation (ie, the White Matter Model, 1989) is that this syndrome is the result of perturbations of white matter development or disturbance in cerebral myelination at a later point in development. Alterations in white matter have been, in fact, the principal finding in both pathological²⁵ and neuroimaging studies of subjects with the more mildly affected late-onset OTCD.^{29,30} A few neuroimaging studies of subjects with late-onset OTCD have been published and have shown localized abnormality in the right cerebral hemisphere.^{31,32}

When we compared our symptomatic to asymptomatic OTCD group, the asymptomatic group (as defined by either clinical symptoms or urea synthetic capacity) outperformed the symptomatic group on all the domains of neuropsychological functioning. There was

also a correlation between residual urea synthetic capacity and some of the domains. We did not, however, find a significant correlation between mutation type (neonatal vs late onset) and residual urea synthetic capacity or cognitive deficits.

In summary, we found a specific neuropsychological phenotype in women who were mildly affected with OTCD. The converging evidence from neuropsychological, neuropathological, and limited neuroimaging studies of this disorder implicates white matter functioning. This provides a model to test our understanding of the underlying mechanisms of hyperammonemic-induced brain damage. Identifying a specific neuropsychological phenotype also allows us to measure the effects of novel treatments. From a developmental standpoint, it helps identify the unique educational needs of children with OTCD who are at risk for learning difficulties. Finally, the study emphasizes the importance of maintaining scrupulous metabolic control in patients with urea cycle disorders who are at significant risk for cognitive deficits.

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