

## NEUROLOGIC OUTCOME IN CHILDREN WITH INBORN ERRORS OF UREA SYNTHESIS

### Outcome of Urea-Cycle Enzymopathies

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**Abstract** We studied 26 children with inborn errors of urea synthesis who survived neonatal hyperammonemic coma. There was a 92 per cent one-year survival rate associated with nitrogen-restriction therapy and stimulation of alternative pathways of waste nitrogen excretion. Seventy-nine per cent of the children had one or more developmental disabilities at 12 to 74 months of age; the mean IQ was  $43 \pm 6$ . There was a significant negative linear correlation between duration of Stage III or IV neonatal hyperammonemic coma and IQ at 12 months ( $r = -0.72$ ,

$P < 0.001$ ) but not between the peak ammonium level ( $351$  to  $1800 \mu\text{M}$ ) and IQ. There was also a significant correlation between CT abnormalities and duration of hyperammonemic coma ( $r = 0.85$ ,  $P < 0.01$ ) and between CT abnormalities and concurrent IQ ( $r = -0.75$ ,  $P < 0.02$ ). These results suggest that prolonged neonatal hyperammonemic coma is associated with brain damage and impairment of intellectual function. This outcome may be prevented by early diagnosis and therapy. (N Engl J Med 1984; 310:1500-5.)

**I**NHERITED deficiencies of each of the five enzymes of the urea cycle have been described. The overall prevalence is estimated to be 1 in 30,000 live births. Unable to excrete waste nitrogen as urea, affected infants accumulate ammonia and other nitrogenous compounds. Children born with a complete deficiency of one of the urea-cycle enzymes (apart from arginase deficiency) appear normal during the first 24 hours of life, but by one week of age symptoms of hyperammonemia develop. These include feeding intolerance, vomiting, lethargy, respiratory distress, seizures, and coma. Previous therapy included modification of the quality and quantity of dietary nitrogen and was associated with a 14 per cent one-year survival rate.<sup>1</sup>

We have proposed combining nitrogen restriction with the stimulation of alternative pathways of waste nitrogen excretion (Fig. 1). Although urea is the normally excreted waste nitrogen product, other nitrogenous compounds may be synthesized and excreted. Two classes of such nonurea nitrogenous metabolites are the cytosolic urea-cycle intermediates and certain amino acid acylation products. In defects of argininosuccinate synthetase (citrullinemia) and argininosuccinase (argininosuccinic aciduria), the synthesis and excretion of citrulline and argininosuccinic acid as waste nitrogen products may be promoted by dietary arginine supplementation. The amino acid acylation products of sodium benzoate and sodium phenylacetate (hippurate and phenylacetylglutamine, respectively) may substitute for urea nitrogen excretion in all urea-cycle defects.

We have used alternative-pathway therapy to treat 26 children with urea-cycle enzyme deficiencies.<sup>2</sup> There has been a 92 per cent one-year survival rate. The neurologic and developmental outcomes in these

children at ages 12 to 74 months (mean, 31) are reported here. Most of the children were handicapped. There was a significant negative linear correlation between duration of neonatal hyperammonemic coma and IQ at 12 months. Significant relationships were also found between abnormalities identified by CT scans of the brain and duration of neonatal hyperammonemic coma and between CT abnormalities and IQ score.

## METHODS

### Subjects

Twenty-six children with complete urea-cycle enzyme deficiencies were identified because of neonatal hyperammonemic coma; carbamyl phosphate synthetase was deficient in three, ornithine transcarbamylase in seven, argininosuccinate synthetase in eight, and argininosuccinase in eight. Two of the male infants with a deficiency of ornithine transcarbamylase died of hyperammonemic coma before one year of age, but the other 24 patients (92 per cent) survived. These 24 children were studied neurologically and developmentally.

### Laboratory Methods

We have previously described our protocol for the management of hyperammonemic coma and long-term therapy using alternative pathways of waste nitrogen excretion.<sup>3</sup> The current management protocol is summarized in Table 1. In addition to sodium benzoate, we have recently added sodium phenylacetate to treat deficiencies of carbamyl phosphate synthetase, ornithine transcarbamylase, and in some cases argininosuccinate synthetase. We also now substitute citrulline for arginine as an essential amino acid in patients with carbamyl phosphate synthetase or ornithine transcarbamylase deficiency.

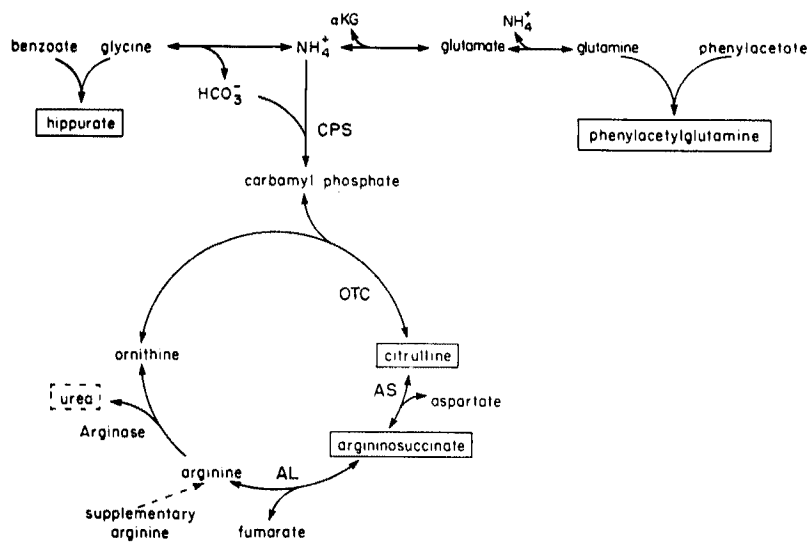
Plasma ammonium levels were measured either by an enzymatic method, using glutamate dehydrogenase,<sup>4</sup> or by a cation-exchange-resin method.<sup>5</sup> Normal plasma ammonium levels, according to these methods, are 15 to 35  $\mu\text{M}$  (20 to 50  $\mu\text{g}$  per deciliter).

### Definitions

Duration of coma was defined as the number of days spent in Stage III or Stage IV coma.<sup>5</sup> Stage III coma was defined as unconsciousness with decerebrate posture and withdrawal response to painful stimuli. Stage IV coma was defined as flaccid tone with dilated unresponsive pupils and no response to painful stimuli. Mental retardation<sup>6</sup> was defined as an IQ under 70. Cerebral palsy was defined as a delay in attainment of motor milestones associated

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**Figure 1. The Urea Cycle and Alternative Pathways of Waste Nitrogen Excretion.** Complete deficiencies in carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), and argininosuccinase (AL) lead to decreased urea synthesis and neonatal hyperammonemic coma. Long-term therapy relies on nitrogen restriction and stimulation of alternative pathways of waste nitrogen excretion. Arginine supplementation stimulates the synthesis and excretion of citrulline in citrullinemia (AS deficiency) and of argininosuccinate in argininosuccinic aciduria (AL deficiency). In CPS and OTC deficiencies, sodium benzoate acylates glycine to form hippurate, and sodium phenylacetate acetylates glutamine to form phenylacetylglutamine. Both waste nitrogen products (shown as boxed compounds) are readily excreted in urine.

with abnormalities in tone or posture and with persistence of primitive reflexes. Seizure disorder was defined as recurrent seizure activity and abnormal electroencephalographic findings in the presence of normal plasma ammonium levels.

**Developmental Assessment**

IQ was determined using the following psychometric tests: Bayley Scales of Infant Development (6 to 30 months), Stanford-Binet Scales (30 to 54 months), and Wechsler Preschool and Primary Scale of Intelligence (54 to 74 months). Testing was performed at least six months after the neonatal hyperammonemic episode and

during a period of normal or nearly normal ammonium levels (<60 μM). Psychometric testing was generally repeated at 6- to 12-month intervals.

**Computed Tomography**

CT studies of the brain were performed without contrast enhancement, using either a Siemens Somatom DR3 or an AS & E Pfizer 500 scanner, in 11 patients evaluated at Johns Hopkins Hospital: one with deficient carbamyl phosphate synthetase, four with deficient ornithine transcarbamylase, three with deficient argininosuccinate synthetase, and three with deficient argininosuccinase. Scans were performed when patients were between 6 weeks and 74 months of age (mean ±S.D., 18±20 months) and were clinically stable.

CT scans of the brain were rated on the prominence of cortical sulci, ventricular dilatation, and brain-substance lucency (Table 2). The scoring system ranged from 0 (normal) to 9 (severe ventriculomegaly with white-matter and cortical abnormalities). Ratings were done by two neuroradiologists who were unaware of the child's clinical history. The reliability index between the neuroradiologists was 82 per cent. IQ testing was performed within 6 months of the CT scan so that the IQ and CT rating could be correlated.

Figure 2 consists of three scans illustrating the spectrum of abnormalities. Scan A is from a 34-month-old boy with ornithine transcarbamylase deficiency. He was in Stage III neonatal hyperammonemic coma for three days, with a peak ammonium level of 450 μM. His IQ was 77 at 24 months of age. Neurodevelopmental examination revealed an attention-deficit disorder with hyperactivity. There was mild ventricular dilatation on the CT scan obtained at 24 months of age; the CT rating was 1. Scan B is from a 51-month-old boy with argininosuccinase deficiency who was in Stage III neonatal hyperammonemic coma for three days, with a peak ammonium level of 1280 μM. His IQ was 55 at 11 months of age. The child had microcephaly. A CT scan obtained at six months of age revealed a small increase in ventricular size and patchy areas of parenchymal low density; the CT rating was 2.5. Scan C is from a 19-month-old argininosuccinase-deficient patient who was in neonatal hyperammonemic coma with increased intracranial pressure for seven days, with a peak ammonium level of 600 μM. She was profoundly mentally retarded, with an IQ of 10 when tested at 14 months of age. Development remained at a newborn level. She also had cerebral palsy, microcephaly, blindness, and a seizure disorder. There were no recurrent episodes of hyperammonemic coma. At 14 months of age the CT scan showed ventriculomegaly, prominent sulci, and subcortical low-density areas and was rated 5.

**Statistical Methods**

In addition to Student's t-test and chi-square analyses, the following polynomial regression analyses were calculated: (1) duration of coma versus IQ at 12 months, (2) CT-scan rating versus concurrent IQ, (3) CT-scan rating versus duration of hyperammonemic coma, (4) peak ammonium level versus IQ at 12 months, and (5) peak ammo-

**Table 1. Regimen for Long-Term Treatment of Patients with Inborn Errors of Urea Synthesis.\***

DEFICIENT ENZYME	NATURAL PROTEIN	ESSENTIAL AMINO ACIDS †	CITRULLINE	ARGININE	SODIUM BENZOATE ‡	SODIUM PHENYLACETATE §
<i>grams per kilogram per day</i>						
CPS	0.6	0.6	0.18	—	0.25	0.25
OTC	0.6	0.6	0.18	—	0.25	0.25
AS	1.2-1.5	—	—	0.4-0.7	0.25	0.25
AL	1.2-1.5	—	—	0.4-0.7	—	—

\*Calories supplemented with Mead Johnson Product 80056, to provide 120 kcal per kilogram of body weight per day. CPS denotes carbamyl phosphate synthetase, OTC ornithine transcarbamylase, AS argininosuccinate synthetase, and AL argininosuccinase.

†Folate (0.1 to 0.5 mg per day) and pyridoxine (5 mg per day) were given with sodium benzoate.

‡Contains the following essential amino acids (g/kg/day):

l-histidine	0.04	l-methionine	0.03
l-isoleucine	0.07	l-phenylalanine	0.07
l-leucine	0.13	l-threonine	0.06
l-lysine	0.11	l-tryptophan	0.03
		l-valine	0.06

§Sodium phenylacetate was introduced in 1982.

**Table 2. Rating Scales for Cerebral Abnormalities Demonstrated by CT Scan.**

Cortical sulci	0 = normal 1 = minimally prominent 2 = moderately prominent 3 = markedly prominent
Ventricles	0 = normal 1 = minimally dilated 2 = moderately dilated 3 = markedly dilated
Brain substance	0 = normal 1 = subcortical low density 2 = scattered areas of low density 3 = confluent areas of low density

nium level versus CT-scan rating. The peak ammonium level was defined as the highest recorded plasma ammonium level during neonatal coma; peak values in the patients have been reported previously.<sup>2</sup> Excluded from these analyses (other than CT versus concurrent IQ) were two patients who were in a coma for 12 and 30 days.

In addition, a paired t-test was used to determine the significance of changes in IQ from 12 months to follow-up at 19 to 74 months. Excluded from this analysis were the four children younger than 18 months. Also excluded was a child who had an episode of hyperammonemic coma at 12 months, associated with Stage IV coma and increased intracranial pressure. This child's IQ fell from 78 to 10 and was deemed outside the range we were considering clinically.

This study was performed between 1978 and 1982 and involved a collaborative effort among 26 medical institutions in the United States and Europe. Parental consent was obtained, and the study was approved by the Joint Committee on Clinical Investigation at Johns Hopkins Hospital and by the institutional review boards of participating hospitals.

## RESULTS

### Mortality

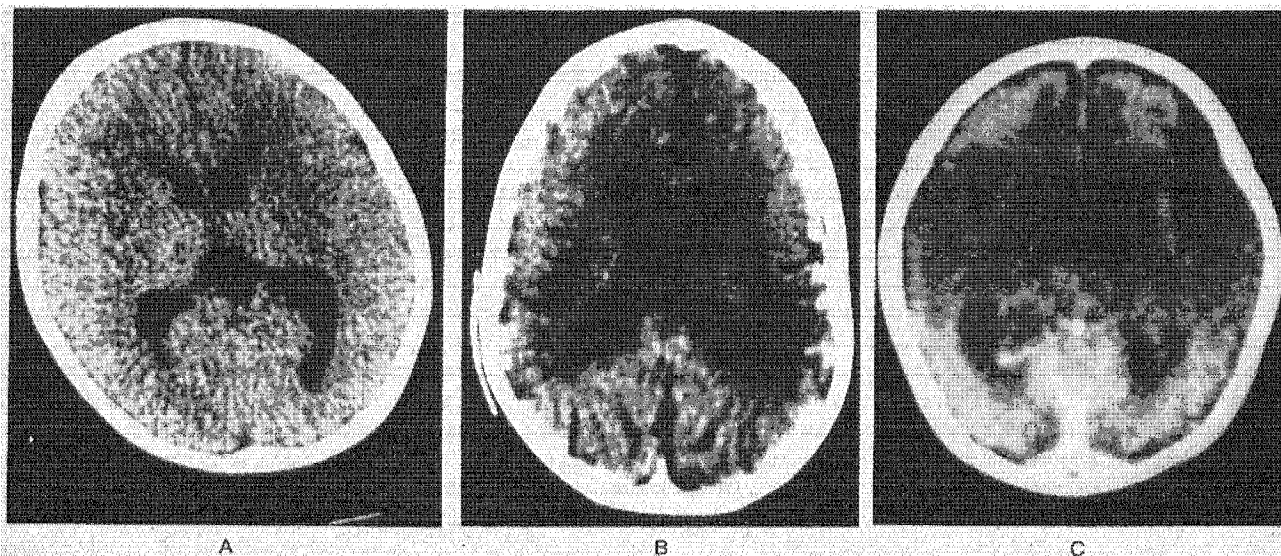
Six of 26 patients died during the study. Two male infants with ornithine transcarbamylase deficiency

died before one year of age and are not included in this paper. Four additional patients who have since died are included: one deficient in carbamyl phosphate synthetase, one in ornithine transcarbamylase, one in argininosuccinate synthetase, and one in argininosuccinase. Two of the deaths resulted from intercurrent hyperammonemic coma, one occurred after an accidental 10-fold overdose of intravenous sodium benzoate and sodium phenylacetate during an episode of hyperammonemia, and one resulted from aspiration pneumonia. Postmortem examinations were not permitted in any of these children.

### Neurologic Function

Table 3 shows that of the 24 children, 19 (79 per cent) had one or more developmental disabilities: 46 per cent had cerebral palsy, 79 per cent were mentally retarded, 17 per cent had seizure disorders, 54 per cent had microcephaly, and one child was blind; 46 per cent had more than one handicapping condition. The most recent IQ was  $43 \pm 6$  (mean  $\pm$  S.E.M.). Twenty-one per cent (five) of the children had an IQ above 70; broken down by type of deficiency, the percentages of children with an IQ above 70 were as follows: carbamyl phosphate synthetase, 0 per cent; ornithine transcarbamylase, 60 per cent; argininosuccinate synthetase, 12 per cent; and argininosuccinase, 12 per cent. Four of these five children had an attention-deficit disorder. A paired t-test was performed on the change between IQ at 12 months and the most recent IQ (mean,  $35 \pm 4$  months; range, 19 to 74) in 19 children. The IQ decreased by  $8.6 \pm 2.5$  points ( $P < 0.01$ ) during this period.

Figure 3 shows the relation between duration of Stage III or IV neonatal hyperammonemic coma and



**Figure 2. CT Scans in Three Children with Complete Urea-Cycle Enzyme Deficiencies.**

Scan A shows mildly dilated ventricles (CT rating, 1.0) in a 24-month-old child with a deficiency of ornithine transcarbamylase. Scan B shows mild ventriculomegaly and patchy areas of parenchymal low density (CT rating, 2.5) in a six-month-old infant with argininosuccinase deficiency. Scan C shows ventriculomegaly, prominent sulci, and subcortical low-density areas (CT rating, 5.0) in a 14-month-old child with argininosuccinase deficiency.

**Table 3. IQ and Developmental Disabilities in 24 One-Year Survivors of Neonatal Hyperammonemic Coma.**

DEFICIENT ENZYME *	NO. OF PATIENTS	AGE (Mo)	DURATION OF COMA (DAYS)	IQ AT 12 Mo	MOST RECENT	DEVELOPMENTAL DISABILITIES (%) †
				<i>mean ± S.E.M.</i>		
CPS	3	19±5	12±9	58±24	39±15	100
OTC	5	21±4	3±1	70±12	56±18	40
AS	8	30±4	5±1	44±10	37±10	88
AL	8	41±7	3±1	50±7	41±8	88
Total	24	31±3	5±1	53±6	43±6	
Range		12-74	1-30	10-100	10-100	

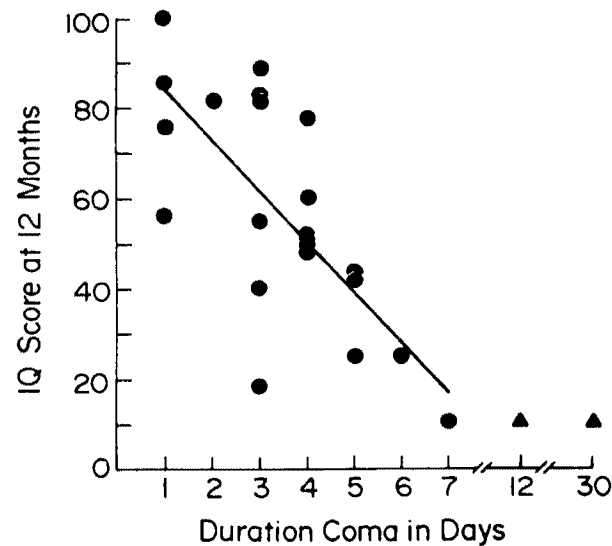
\*CPS denotes carbamyl phosphate synthetase, OTC ornithine transcarbamylase, AS argininosuccinate synthetase, and AL argininosuccinase.

†Developmental findings for the group as a whole were as follows: normal function, 21 per cent; mental retardation, 79 per cent; cerebral palsy, 46 per cent; seizure disorder, 17 per cent; blindness, 4 per cent; microcephaly, 54 per cent; and multiple handicaps, 46 per cent.

IQ at 12 months of age. There was a significant negative linear correlation ( $r = -0.72$ ,  $y = -11x + 95$ ,  $P < 0.001$ ); the longer the duration of coma, the more likely that the child would be mentally retarded. Four of the five children, whose duration of coma was two days or less had normal IQ scores at 12 months, whereas all seven children whose duration of coma was five days or more were mentally retarded. There was no significant correlation between peak ammonium level (351 to 1800  $\mu\text{M}$ ) and IQ score at 12 months.

**Computed Tomography**

CT scans were performed in 11 children studied at the Johns Hopkins Hospital. Figure 4 shows the relation between CT rating and concurrent IQ score. There was a significant negative linear correlation ( $r = -0.75$ ,  $y = -9.8x + 76$ ,  $P < 0.02$ ). There



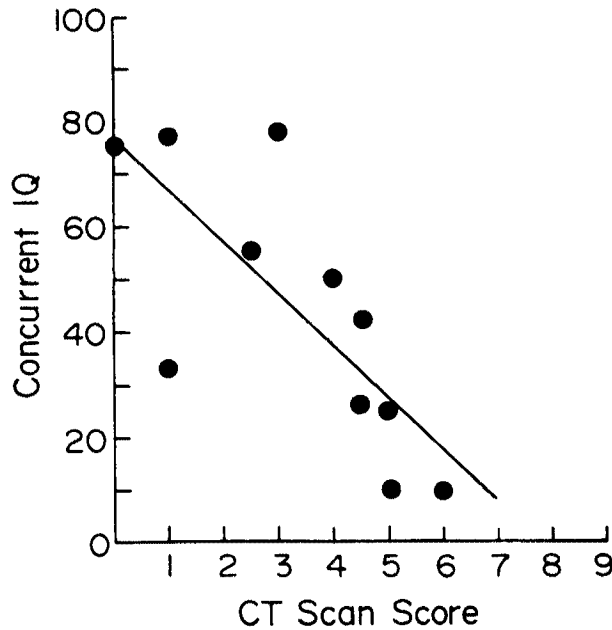
**Figure 3. Relation between Duration of Neonatal Hyperammonemic Coma and IQ at 12 Months of Age ( $r = -0.72$ ,  $y = -11x + 95$ ,  $P < 0.001$ ,  $n = 22$ ).**

The triangles indicate two children who were in coma for 12 to 30 days.

was also a significant linear correlation between duration of coma and CT-scan rating ( $r = 0.85$ ,  $Y = 0.98x - 0.97$ ,  $P < 0.01$ ; Fig. 5). There was no significant correlation between peak ammonium level during hyperammonemic coma and CT rating.

**DISCUSSION**

It was not previously possible to perform a long-term follow-up study of patients with congenital urea-cycle enzyme deficiencies, because of the poor one-year survival rate. In 1976 Shih<sup>1</sup> reviewed the outcome in patients with complete urea-cycle enzyme deficien-



**Figure 4. Relation between CT Abnormality Rating and Concurrent IQ ( $r = -0.75$ ,  $y = -9.8x + 76$ ,  $P < 0.02$ ,  $n = 11$ ).**

cies before the use of alternative-pathway therapy. Among 28 patients (5 deficient in carbamyl phosphate synthetase, 10 deficient in ornithine transcarbamylase, 6 deficient in argininosuccinate synthetase, and 7 deficient in argininosuccinase) the one-year survival rate was 14 per cent. Three of the four survivors were mentally retarded.

In our study, there was a 92 per cent one-year survival rate among 26 patients with complete urea-cycle enzyme deficiencies treated with a combination of nitrogen restriction and supplements of sodium benzoate, arginine, citrulline, and more recently, sodium phenylacetate. Although survival improved, neonatal hyperammonemic coma had a devastating effect (Table 3). Seventy-nine per cent of our patients had at least one developmental disability, and 46 per cent had multiple handicaps (some combination of mental retardation, cerebral palsy, and seizures) when evaluated at ages ranging from 12 to 74 months.

Ammonia has been implicated as a neurotoxin in a

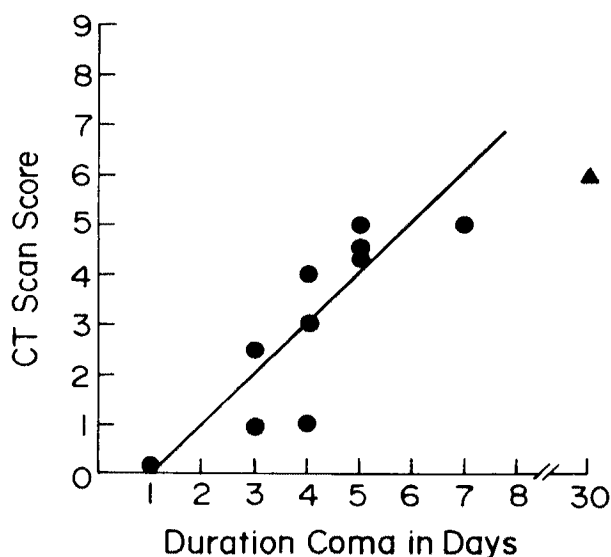


Figure 5. Relation between Duration of Neonatal Hyperammonemic Coma and CT Abnormality Rating ( $r = 0.85$ ,  $y = 0.98x - 0.97$ ,  $P < 0.01$ ,  $n = 10$ ).

The triangle indicates a child who was in coma for 30 days and is not included in the correlation.

number of disorders, including portal-systemic encephalopathy,<sup>7</sup> Reye's syndrome,<sup>8</sup> and urea-cycle enzyme deficiencies. The pathophysiology of ammonia toxicity, although unclear, has been variously ascribed to increased permeability of the blood-brain barrier, depletion of intermediates in energy metabolism, and a cytotoxic effect on microtubular aggregates, causing disruption of cytoplasmic integrity.<sup>9</sup> In animal models, hyperammonemia (ammonium levels above 1000  $\mu\text{M}$ ) leads to reversible swelling of astrocytes and increased intracranial pressure.<sup>10</sup>

Survivors who are severely mentally retarded have chronic neuropathological findings, including increased ventricular size, areas of focal cortical necrosis, and frontal-parietal atrophy.<sup>11-15</sup> Myelination has been variously described as normal or deficient. These findings may reflect hypoxia, hypovolemia, and increased intracranial pressure, as well as the precipitating hyperammonemia. Thus, the associations we found between duration of coma and brain damage may reflect all these factors. In fact, one of our patients had a cardiopulmonary arrest, and a number had respiratory distress or increased intracranial pressure or both during neonatal hyperammonemic coma.

CT findings in patients with urea-cycle disorders have been consistent with the neuropathological findings. Kendall et al.<sup>16</sup> noted cerebral atrophy, ventriculomegaly, and low-density white matter in seven mentally retarded patients with partial ornithine transcarbamylase deficiency. We noted similar CT abnormalities in our patients with complete urea-cycle enzyme defects. We also found a significant correlation between CT abnormalities and duration of neonatal hyperammonemic coma. Furthermore, the IQ

scores at 12 months were directly correlated with the length of time in neonatal hyperammonemic coma. A good prognosis was observed in patients with coma lasting less than three days. In this group, four of five children had a normal IQ. Conversely, patients in Stage III or IV coma for more than five days were invariably handicapped. The peak ammonium level (between 351 and 1800  $\mu\text{M}$ ) was not correlated with IQ at 12 months. A multivariate analysis indicated that the peak ammonium level did not add to the significance of the association between duration of coma and IQ at 12 months. However, with a sample size this small nonsignificant results should not be interpreted as indicating that the relation does not exist. Part of the effect of the small sample size is reflected in the relatively large variation indicated by the calculated standard error of the mean in Table 3. Despite the fact that all these infants had complete or nearly complete enzyme deficiencies,<sup>2</sup> the possibility remains that small variations in residual enzyme activity may have played a part in the ultimate outcome.

A comparison between IQ at 12 months and at follow-up (19 to 74 months) showed a mean decrease of 8.6 points. It is unclear whether this decline in IQ was clinically important, since it occurred in patients who were already handicapped.<sup>17-19</sup> If so, the decrease may have been attributable to one or more of the following factors: intercurrent hyperammonemic episodes, drug toxicity, toxicity of citrulline or argininosuccinic acid, or inadequate infant stimulation or nutrition.

This study indicates an association between the duration of Stage III or IV neonatal hyperammonemic coma and brain damage, as evidenced by abnormalities on CT scan. The findings indicate a similar association between duration of coma and future intellectual function. Therefore, one might speculate that unless therapy is started during the earliest stages of hyperammonemic coma in infants, most will be severely handicapped.

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