Plasma glutamine concentration: A guide in the management of urea cycle disorders

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Because increases in plasma glutamine concentrations are almost always associated with hyperammonemia in patients with urea cycle disorders, we determined the correlation between these two variables for 2 years in a child with ornithine transcarbamylase deficiency. A correlation coefficient of 0.77 ($p < 0.0001$) was found. Hyperammonemia was rarely observed when plasma glutamine levels were near normal. These data suggest that one goal of therapy is the maintenance of plasma glutamine levels at or near normal values. (J PEDIATR 1992;121:259-61)

The presence of hyperglutaminemia in hyperammonemic patients with urea cycle disorders has been known since the earliest case reports[1] and is another manifestation of the disorder of nitrogen homeostasis.[2, 3] Moreover, in two patients with ornithine transcarbamylase deficiency, plasma glutamine levels increased before the onset of hyperammonemia.[4] Hyperglutaminemia is also associated with the hyperammonemia of severe liver disease[5] and Reye syndrome.[6] On the basis of these observations, this study examined the relationship between the plasma glutamine and ammonium concentrations during a 24-month period in one patient with the neonatal form of OTC deficiency.

CASE REPORT

The patient was the younger brother of a boy with OTC deficiency who, after rescue from neonatal hyperammonemic coma, was profoundly developmentally delayed and died in hyperammonemic coma at age 16 months of age. The mother was identified as a carrier of the mutation at the OTC locus on the basis of the diagnosis of the proband and a positive protein tolerance test result. More recently, the mutation in this pedigree has been identified as a T→C substitution in the initial dinucleotide of intron 7, resulting in a deletion of exon 7.[7] The family was lost to follow-up until the mother was 26 weeks' pregnant with a fetus of unknown gender. After genetic counseling, during which the options for diagnosis and treatment were described, [8] the family chose delivery at their local community hospital and declined to enter the infant into an experimental diagnostic and treatment protocol. After delivery, notwithstanding the earlier decision, the apparently healthy term male neonate was not fed enterally but was given only intravenous fluids including 10% glucose solution. On discharge from the community hospital when the infant was 48 hours of age, the parents chose to seek therapy and the patient was brought directly to Johns Hopkins Hospital. On arrival he was lethargic and had plasma ammonium and glutamine levels, respectively, of 117 and 2074 μmol/L (normal values <30 and 613 ± 15)[9]; plasma citrulline was undetectable. He also had a plasma orotate level of 2.13 μmol/L (undetectable in normal neonates [Brusilow SW: unpublished observations]) and a respiratory alkalosis. After further counseling, the parents gave informed consent for the patient's entry into a study evaluating the intravenous dosage form of benzoate and phenylacetate, and long-term therapy with the oral dosage form of sodium phenylbutyrate. At 24 and 48 hours after intravenous therapy,[10] the patient's plasma ammonium levels were, respectively, 31 and 24 μmol/L.

OTC	Ornithine transcarbamylase

In the subsequent 2 years the patient has been treated with a low protein diet (at times supplemented with essential amino acids), L-citrulline, 175 mg/kg per day, and sodium phenylbutyrate, 500 to 600 mg/kg per day. The details and variations of this protocol are described elsewhere.[10] On the Cattell Infant Intelligence Scale his development quotient was 80 at 19 months of age. The patient is at the 25th percentile for weight and below the 3rd percentile for height. He has been admitted to the hospital three times because of symptomatic hyperammonemia.

METHODS

During the 2-year follow-up period, 57 measurements were made of plasma ammonium and amino acid levels. In-

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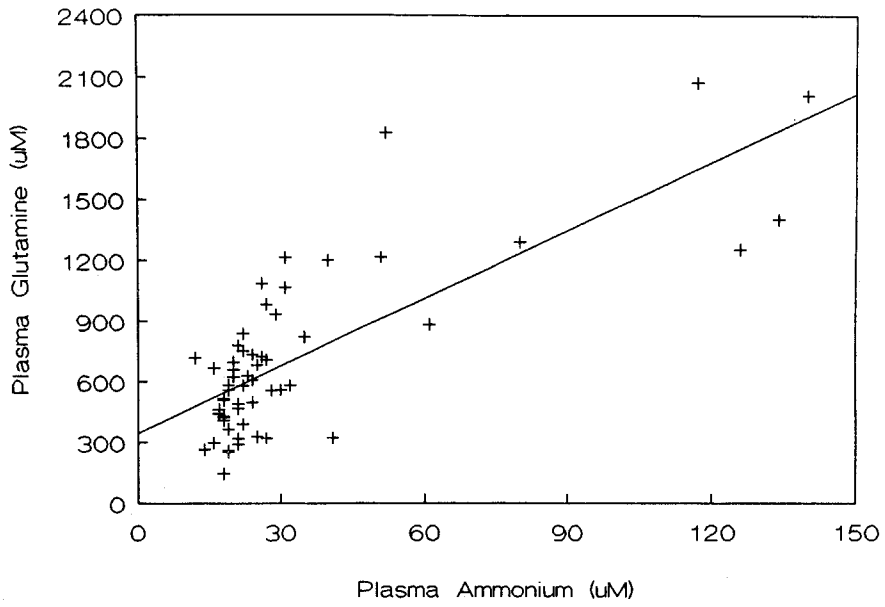

Figure. Relationship between plasma glutamine and ammonium concentrations. For all values the Pearson correlation coefficient is 0.77 (p <0.0001). For plasma ammonium values less than 30 μmol/L (ρ = 0.436; p <0.0001).

cluded in this study are those values obtained during all outpatient visits. Plasma ammonium levels were measured by a cation exchange–visible spectrophotometric technique,[11] and plasma amino acids were measured by automated column chromatography using a Beckman model 6300 amino acid analyzer (Beckman Instruments, Inc., Brea, Calif.). Apart from the initial sample, blood was collected from the patient during daytime hours (plasma glutamine levels are lowest then in patients treated with this protocol[12]). Blood was placed in heparinized tubes and immediately chilled on ice, and the plasma was promptly separated in a refrigerated centrifuge and analyzed immediately or frozen for analysis within 24 hours.

RESULTS

The relationship between plasma levels of ammonium and glutamine in this patient is shown in the Figure. The Pearson correlation coefficient for all values of glutamine and ammonium was calculated as 0.77 (p <0.0001). When plasma ammonium levels were within the normal range (<30 μmol/L), glutamine levels varied between 145 and 1090 μmol/L and were more weakly correlated with plasma ammonium levels (ρ = 0.436; p <0.0001).

Plasma glutamine measurements were grouped into six strata, and the mean glutamine and ammonium levels were calculated. As shown in the Table, the mean ammonium level was normal for glutamine values less than 800 μmol/L; however, when plasma glutamine levels increased above this level, an increasing percentage of ammonium levels were high. Furthermore, the height of the plasma ammonium level was strongly correlated with the height of the plasma glutamine concentration.

DISCUSSION

The findings of a weaker correlation between plasma ammonium and glutamine levels when plasma ammonium levels are normal are consistent with the hypothesis that increased plasma glutamine levels are forerunners of increased plasma ammonium levels.[4] These data, in conjunction with the reports cited earlier, suggest that glutamine may represent a storage site for nitrogen accumulation. The precise capacity of glutamine to serve this function is unknown, but it appears that as plasma glutamine levels increase to greater than normal, there is a greater likelihood of hyperammonemia. Although the plasma level of glutamine above which ammonium accumulated in this patient was approximately 1000 μmol/L, our random observations of other patients suggest, as might be expected, that there may be considerable individual variability of this threshold.

These data have potentially useful monitoring and therapeutic implications. They suggest that increasing plasma glutamine levels may indicate that dietary or drug therapy requires modification. Such modifications include an increased dose of phenylbutyrate, an increased calorie intake, a reduction of total nitrogen intake, and redistribution of nitrogen intake between natural protein and essential amino acids to take advantage of the lower nitrogen density of essential amino acids.

Table. Number of high (>30 μmol/L) plasma ammonium levels for specified plasma glutamine levels

Range of Gln (μmol/L)	n	Mean Gln (μmol/L)*	Mean NH_4^+ (μmol/L)*	NH_4^+ >30 μmol/L	
				No.	%
200-400	12	295 ± 62.8	21.8 ± 7.0	1	8
401-600	16	503 ± 61.3	21.3 ± 4.8	1	6
601-800	13	690 ± 51.8	21.5 ± 4.1	0	0
801-1000	5	892 ± 66.8	34.8 ± 15.4	2	40
1001-1400	7	1190 ± 84.0	55.0 ± 36.3	6	86
>1400	4	1829 ± 302.8	110.8 ± 40.4	4	100

Gln, Glutamine; NH_4^+, ammonium.
*Values are mean ± SD.

These findings may have broader significance in view of recent reports suggesting that glutamine may be more closely related to the pathophysiology of the encephalopathy of hyperammonemia than is ammonium.[13, 14]

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