SIGNIFICANCE OF BLOOD AMMONIA IN UREMIC ENCEPHALOPATHY

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ABSTRACT:

***Aim of the study**: To determine the role of blood ammonia in uremic encephalopathy, and its correlation with other uremic toxins involved in renal failure.*

***Methodology**: The study group included 30 apparently normal individuals and 15 patients with clinically diagnosed uremic encephalopathy in the age group of 30-50 years. Peripheral venous sample was used for the study. Blood ammonia was estimated by Berthelot-Indophenol method.; blood urea by modification of Diacetyl Monoxime method, serum creatinine by modified Jaffe reaction, serum sodium and potassium by flame photometry, serum calcium by modification of cresolphthaline complexon method, and serum phosphorus by modification by Wang et al. Student 't' test was used to find out statistical significance.*

***Results**: The various biochemical parameters were compared using student 't' test with significance of 'p' value at 0.05. Blood ammonia was found to be 70.16 ± 9.11µmol/L in the control subjects. In uremic encephalopathy the level was found to be 78.61 ± 24.42µmol/L.*

***Conclusion**: Blood ammonia was found to be normal in uremic encephalopathy and that it could not be involved in its pathogenesis. Urea and creatinine still remain to be the markers of uremic encephalopathy.*

***Key words:** uremic encephalopathy, uremia, uremic toxins, blood ammonia, hyperammonemia, astrocytosis.*

SRJM 2009 : I (14 - 16)

INTRODUCTION:

Uremic encephalopathy describes the final stage of progressive renal insufficiency, which culminates in end-stage kidney failure with neurological involvement (1,2,3,4). Under conditions of renal failure where the blood level of urea is high, the amount of urea entering the renal vein and subsequently into the gut is high(5). This is acted upon by urease produced by colonic bacteria converting it to ammonia. Urea acts as a uremic toxin only at extreme levels. At such levels it inhibits argininosuccinate lyase and could exert feedback inhibition of urea production possibly by channeling waste nitrogen into more toxic compounds like ammonia, carbamate or cyanate(6,7,8,9,10). Though ammonia is toxic, systemic blood ammonia levels are normal or only minimally elevated in uremia. Some of the symptoms of uremia especially nausea, vomiting, malaise and possibly bleeding are partly due to its intoxication with urea or a product of urea metabolism which could be ammonia(10,11). The present study was done to find out the significance of blood ammonia in uremic encephalopathy.

Materials and methods

The study was performed on the venous blood of 30 subjects who were apparently normal males and females in equal number. The control group was from the staff of Madras Medical College and Government Hospital belonging to the age group of 30-50 years. The subjects of the diseased group, 15 in number were the patients undergoing treatment in the nephrology department in Madras Medical College. These patients were clinically diagnosed to have uremic encephalopathy. Fasting venous samples were collected after obtaining consent from the patients. The samples were analyzed to estimate ammonia, urea, creatinine, sodium, potassium, calcium and phosphorus.

Estimation of ammonia: Berthelot-Indophenol method (Wako Pure Chemicals) (12,13,14). Berthelot's reagent is an alkaline solution of phenol & hypochlorite. Ammonia reacts with Berthelot's reagent to form a blue product which is estimated.

Reference value: arterial blood: 22-61µmol/L (as per the method). Several recent studies have suggested that it is not necessary to utilize arterial blood when measuring ammonia in blood. Venous blood or a computation of the partial pressure of ammonia in blood sample may suffice. All the older methods have the reference values based on the arterial sample. Only recently venous samples have been used instead of arterial samples because of ease of collection, less trauma and other advantages. Hence arterial blood reference values are given as per the used methodology (16).

Estimation of blood urea by modification of Diacetyl Monoxime method(17,18). Estimation of serum creatinine by modified Jaffe reaction(19). Estimation of serum sodium and potassium by flame photometry (ELICO CL 26D)(20). Estimation of serum calcium by

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modification of cresolphthaline complexon(OCP) method of Moorehead and Briggs(20). Estimation of serum phosphorus by modification by Wang et al of Daly and Ertinghausen method(21).

RESULTS:

The results of the various biochemical parameters of all subjects are tabulated in table I. The various biochemical parameters were compared using student 't' test with significance of 'p' value at 0.05. Table I shows the comparison of biochemical parameters between the control and diseased groups. Blood ammonia was found to be $70.16 \pm 9.11 \mu$mol/L in the control subjects. In uremic encephalopathy the level was found to be $78.61 \pm 24.42 \mu$mol/L. All the parameters except ammonia showed significant difference between the two groups. There was no significant alteration in blood ammonia in uremic encephalopathy patients when compared with that of controls. Level of blood ammonia did not show any correlation with other parameters.

DISCUSSION:

Blood ammonia level in patients with uremic encephalopathy did not show significant change when compared with that of controls. Ammonia being largely contributed by the intestine is taken almost completely by the liver where it is detoxified to urea. In patients with uremic encephalopathy with normal liver functions, most of the ammonia is taken by liver. In the kidney small amount of ammonia is formed by the reaction catalyzed by glutaminase. But this source is insignificant in uremia since the functioning nephrons are much reduced in number. Normally about 40% of the urea filtered by the glomeruli is reabsorbed in the proximal convoluted tubule. This urea through systemic circulation reaches intestine. By the action of urease, urea is hydrolyzed to ammonia. But in patients with uremic encephalopathy urea is converted to guanidine compounds instead of ammonia (22-26). Hence, blood ammonia level does not increase significantly in uremic encephalopathy. This is more in accordance with the author,

Table 1: Comparison of biochemical parameters between control group and uremic encephalopathy group

Groups	n	NH_3 μmol/L	Urea mmol/L	Creatinine μmol/L	Sodium mmol/L	Potassium mmol/L	Calcium mmol/L	Phosphorus mmol/L
Control	30	70.16 ± 9.11	12.93 ± 1.47	82.21 ± 8.84	138.96 ± 2.54	4.10 ± 0.39	2.43 ± 0.81	1.46 ± 0.09
UE	15	78.61 ± 24.42#	55.60 ± 9.30***	881.34 ± 200.67***	137.40 ± 1.67*	4.5 ± 0.51**	2.24 ± 0.17***	1.77 ± 0.20***
Values are mean ± SD ***p < 0.001, ** p < 0.01, *p < 0.05, #p > 0.05								

Nancy A Brunzel, (27) who states that unlike the other non-protein nitrogenous substances; concentration of ammonia in the plasma is not a useful indicator of renal function.

Fasting sample is preferable for the estimation of blood ammonia due to the following reasons; the major source of circulating ammonia is the gastrointestinal tract. Plasma ammonia concentration in the hepatic portal vein is typically five to tenfold higher than that in the systemic circulation. It is derived from the action of bacterial proteases, ureases and amine oxidases on the contents of the colon and from the hydrolysis of glutamine in both the small and large intestine. Hence a protein rich diet causes marked elevation in blood ammonia compared to that of fasting state (28).Proteins in the intestine can be broken down by microflora into ammonia, indoles, phenols, amines etc. Urea and creatinine are elevated as a result of reduced glomerular filtration rate (GFR) and decreased tubular function (29).

Retention of these compounds and of metabolic acids is followed by progressive hyperphosphatemia, hypocalcemia and potentially dangerous hyperkalemia as evidenced by our study. Guanidine compounds, especially methyl guanidine, have been implicated in toxicity of experimental renal failure, but their significance in human uremia remains to be found (30). Generally all uremic toxins exert their effect through enzyme inhibition, irreversible carbamoylation of proteins and derangement in membrane transport (31).

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