

AMMONIA & HEPATIC ENCEPHALOPATHY.

Reviewed by,

Dr. Yogesh Waikar

Pediatric Gastroenterologist & Hepatologist.

CARE hospital, Nagpur.

Normal range: 10-80 $\mu\text{g/dl}$ / 5-50 $\mu\text{mol/L}$ Elevated in: Hepatic failure, hepatic encephalopathy, Reye's syndrome, portacaval shunt, drugs (diuretics, polymyxin B, methicillin)

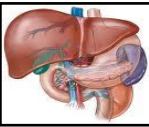
Decreased in: Drugs (neomycin, lactulose, tetracycline), renal failure

An elevation in ammonia with cirrhosis and altered sensorium supports a diagnosis of HE. Blood ammonia levels may be elevated in the absence of HE, because of gastrointestinal bleeding or the medications. Use of a tourniquet when blood is drawn and delayed processing (>15 min) and cooling of a blood sample may raise the blood ammonia level. Measurement of **arterial ammonia offers no advantage over measurement of venous ammonia** levels in patients with **chronic liver disease**. **Acute liver failure, elevated arterial ammonia levels** (150 to 200 mg/dL or higher) may be predictive of the presence of brain edema and herniation. But over all Serum ammonia levels are neither sensitive nor specific indicators.

The importance of measurements of the blood ammonia concentration in the evaluation of patients with known or suspected hepatic encephalopathy (HE) is still disputed in spite of a general acknowledgment that ammonia is important in the pathogenesis of the disorder.

In the brain, glutamine synthesis is largely confined to astrocytes, and it is now generally believed that excess ammonia in the brain leads to an excessive accumulation of glutamine in the astrocytes. One mechanism for ammonia toxicity involves the osmotic effects of excess glutamine leading to cerebral edema. Most of the Clinical laboratories usually do not distinguish between ammonium ions (NH_4^+) and unionized ammonia (NH_3) when determining plasma ammonia, while some ammonia can cross into the brain as NH_4^+ , **unionized ammonia is uniquely able to freely spread through the blood-brain barrier (BBB)** causing neurotoxicity. Ammonia exists in two forms in blood: ammonium ion (NH_4^+) and unionized ammonia (NH_3). At physiological pH values, the pKa for ammonia is about 9.2, and only 1% of ammonia is unionized ammonia. Biological membranes are much more permeable to NH_3 than NH_4^+ , so only NH_3 freely passes through the blood-brain barrier.

How to calculate partial pressure of ammonia:



$$p\text{NH}_3 = \frac{\text{Total ammonia nitrogen}}{\frac{[\text{H}^+]}{K'a} + 1} \times \frac{22.09}{\chi}$$

where $\chi = 0.9$ and $K'a = 9.8 \times 10^{-10}$.¹⁰

Or by Nomograms.

Manning RT. A Nomogram for Estimation of Pnh3. J Lab Clin Med. 1964;63:297–298.

Inability to distinguish between the two forms of ammonia lead to variable results of previous studies on the existence of a correlation between ammonia concentration and severity of hepatic encephalopathy.

Factors leading to increased NH₃ uptake into the brain in hepatic encephalopathy are increased blood ammonia, increased blood pH, increase in the permeability-surface area. Increased blood pH will promote uptake of ammonia into the brain in hepatic encephalopathy patients. **pNH₃ is more appropriate** for evaluating the severity and clinical condition of cirrhotic patients with hepatic encephalopathy than total blood ammonia. **Slow ammonia metabolism** may be the cause of delayed response.

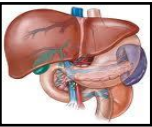
Along with ammonia there are various factors like serotonin (5-hydroxytryptamine, 5-HT), nitric oxide (NO), circulating opioid peptides, manganese, and increased oxygen free radical production **which determine the outcome of hepatic encephalopathy hence the deferred response in cases as well as in studies.** Ideally, one would like to know how much ammonia enters the brain, not how much is in the blood.**1**

In acute liver failure (ALF), the brain is exposed to high levels of ammonia. Human studies defining the clinical significance of ammonia in ALF are lacking and are with controversial results. Arterial ammonia at presentation is predictive of outcome and can be used for risk stratification. Ammonia lowering therapies in patients with ALF should be evaluated.**2**

Chronic hepatitis leading to impairment of glutamine and urea synthesis, reduction of tissue blood flow and oxygen partial pressure due to inhibition activity of glutamate dehydrogenase, arginase and short-term depression activity of phosphate-dependent glutaminase. The changes in the enzymatic activity lead to lowering tissue level of glutamine, urea, and accumulation of ammonia ions**3**

Some authors appears to be of opinion of no additional advantage **4**of measuring the partial pressure of ammonia compared with total ammonia levels while some are in favour.**5**

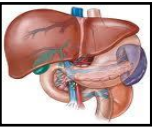
Among cirrhotic patients with hepatic encephalopathy, pH, pNH₃ and ammonia levels were all higher than those among patients without hepatic encephalopathy, and **alkalosis was more common in patients with hepatic encephalopathy.** Both venous ammonia and pNH₃ are significantly correlated to the clinical grade of hepatic encephalopathy.**6**



In acute on chronic liver failure study by Ludwig K et al noted, pH-dependent partial pressure of ammonia correlates more closely than total ammonia with the severity of acute episodes of HE in cirrhotic patients.⁷

References:

1. Lockwood AH .Blood ammonia levels and hepatic encephalopathy. Metab Brain Dis. 2004 Dec ; 19(3-4): 345-9
- 2.Bhatia V, Singh R, et al Predictive value of arterial ammonia for complications and outcome in acute liver failure. Gut. 2006 Jan ; 55(1): 98-104
3. Savilov PN[The ammonia neutralization function of the liver in chronic active hepatitis]. Patol Fiziol Eksp Ter. 2004 Jan-Mar ; : 24-6
4. Ong JP, Aggarwal A, Krieger D etal Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med. 2003 Feb 15; 114(3): 188-93
5. Kramer L, Tribl B, Gendo A etal Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology. 2000 Jan ; 31(1): 30-4
6. Ludwig k, Barbara T, Alexander G ,et al Partial Pressure of Ammonia Versus Ammonia in Hepatic Encephalopathy. Hepatology 2000;31:30-34.



PEDGIHEP

www.pedgihep.jigsy.com

E- mail: pedgihep@yahoo.com