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Diurnal Fluctuation of Blood Ammonia Levels in Adult-Type Citrullinemia

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Yajima, Y., Hirasawa, T. and Saheki, T. *Diurnal Fluctuation of Blood Ammonia Levels in Adult-Type Citrullinemia.* Tohoku J. exp. Med., 1982, **137** (2), 213–220 —— A 48-year-old man, who was diagnosed as adult-type citrullinemia by quantitative estimation of urea cycle enzymes in the liver, showed a regular nocturnal rise of blood ammonia level. In order to elucidate the mechanism of diurnal fluctuation of blood ammonia level, the patient was put into fasting state for four days. The blood ammonia level rose at the night of the first fasting day even though no food was taken, then it decreased gradually and reached the lowest level in the morning of the third fasting day. Intravenous administration of amino acids mixture under the same starved condition gave rise to a significant elevation of blood ammonia level. Based on these results, it was concluded that hyperammonemia of adult-type citrullinemia could result from the accumulation of free ammonia which was produced from the catabolism of amino acids absorbed from the small intestine and surpassed the urea synthesis of defective urea cycle to flood into the blood. Furthermore, the rise of blood ammonia level at the night of the first fasting day suggested that the circadian rhythm of amino acid-carbohydrate metabolim might superimpose on the process mentioned above. adult-type citrullinemia; hyperammonemia; diurnal fluctuation

A 48-year-old man with adult-type citrullinemia has been described in our previous report (Yajima et al. 1981). He showed repetitive episodes of encephalopathy and was diagnosed by quantitative estimation of amino acids and urea cycle enzymes in the liver. In this case, a regular diurnal fluctuation of the blood ammonia level was seen and the drip infusion of glutamate-arginine mixture and oral administration of citrate lowered the blood ammonia level. But the liver function tests of the patient became worse one month after the laparotomy for the evaluation of urea cycle enzymes and he clinically deteriorated to the state of general liver failure with jaundice and ascites. He died two months after the laparotomy. At the stage of general liver failure, citrate ingestion was ineffective and regular diurnal fluctuation of blood ammonia was no longer seen.

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This paper discusses the mechanism of regular diurnal fluctuation of blood ammonia characteristic of this case from the data obtained in a starvation test, ammonia tolerance test, intravenous amino acids loading test and variation of blood ammonia during the period of general liver failure.

Method and Subjects

A case of adult-type citrullinemia and, as controls, five cases of decompensated liver cirrhosis were studied. Case 1 of control group was a 46-year-old male who had a mesocaval shunt operation for the esophageal varices and hypersplenism. Case 2 was a 53-year-old male in whom hepatic encephalopathy appeared following the rupture of the esophageal varices and thereafter encephalopathy of grade 1 to 2 according to Sherlock's classification lasted. Case 3 was a 61-year-old female who was a decompensated cirrhotic patient with a triad of ascites, jaundice and encephalopathy and in whom lactulose administration of 60 ml a day after the onset of encephalopathy lowered blood ammonia level. Case 4 was a 68-year-old female who had intractable ascites refractory to both strict salt restriction and the use of potent diuretics during the three-months' hospitalization. Case 5 was a 40-year-old male who was admitted to our hospital because of ascites and responded well to medical treatment. The ascites was not present at the time of blood ammonia determination. Blood ammonia was measured by the modified method of Okuda and Fujii (1966) (normal range 40–80 μg/100 ml).

Result

Variation of blood ammonia levels in adult-type citrullinemia

The effect of starvation. To prevent the hyperammonemia, protein intake was restricted to less than 50 g a day and the clinical course was observed. Symptoms of encephalopathy and asterixis occurred at night. The blood ammonia was measured four times a day, i.e., 9:00 a.m., 2:00 p.m., 8:00 p.m. and 11:00 p.m. during three consecutive days in order to elucidate the correlation between hyperammonemia and encephalopathy. It revealed that the level of blood ammonia depicted a gentle curve which had its peak between 8:00 p.m. and 11:00 p.m. Blood ammonia was then measured at 9:00 a.m. and 8:00 p.m. every day. The average of fasting levels was 120±38 μg/100 ml at 9:00 a.m. and 430±79 μg/100 ml at 8:00 p.m.

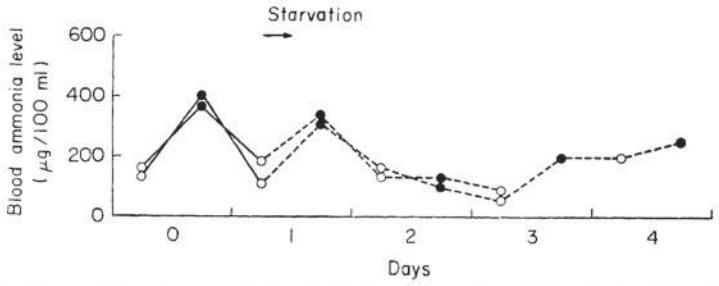

Fig. 1. Variation of blood ammonia levels during starvation. The night of the first fasting day had a rise of blood ammonia level without taking any food, since then it decreased gradually to reach the lowest level in the morning of the third day. ○, levels at 9:00 a.m.; ●, levels at 8:00 p.m. Second starvation trial was stopped on the third fasting day.

In order to investigate the mechanism of the nocturnal rise of blood ammonia level the patient was put into a fasting state for four days. During the starvation period, water, electrolyte and 200 g glucose were supplemented intravenously and the blood ammonia level was measured at 9:00 a.m. and 8:00 p.m. every day. The blood ammonia level rose in the night of the first fasting day, but since then it decreased gradually and reached the lowest level in the morning of the third fasting day. But after the night of the third day the blood ammonia level began to rise again. Another starvation trial under the same condition performed a week later showed the same result.

The effect of intravenous administration of amino acids. Under the same condition as the previous two starvation trials, an amino acids mixture was administered intravenously in the night of the first and the second day and the morning of the third day. The amino acids mixture was a commercially available one which was synthesized after the constituent of the human milk. 500 ml of a 5% solution of the amino acids mixture was administered by drip infusion for 2 hr and the blood ammonia level was measured immediately after the end of the infusion. In each occasion, the blood ammonia levels rose considerably by 100–200 μg/100 ml. In decompensated cirrhotic case (Case 4) with an ascites, three trials of amino acids infusion in the fasting state in the early morning had no influence on the blood ammonia levels.

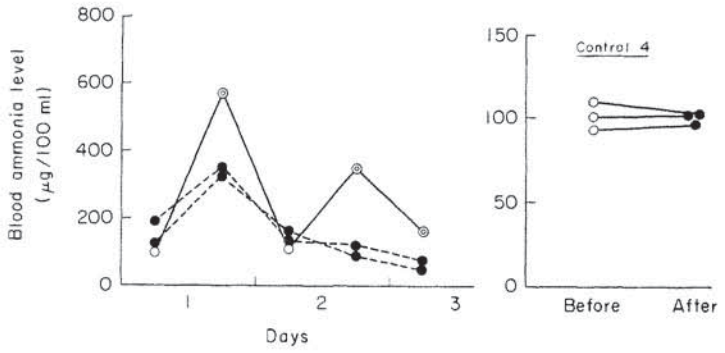

Fig. 2. The effect of the intravenous administration of amino acids mixture during the starvation period. Two broken lines indicate starvation trials without amino acids administration. ◎, blood ammonia levels after amino acids administration.

Ammonia tolerance test. Ammonium chloride, 0.5 g/10 kg body weight, was loaded orally and blood ammonia was measured every half an hour. Blood ammonia had its peak at 60 min after loading and got to the initial value 2 hr later (Fig. 3).

Variation of blood ammonia level during the stage of general liver failure. The liver function tests of the patient became worse a month after the laparotomy for liver biopsy and clinically deteriorated to the state of general liver failure with

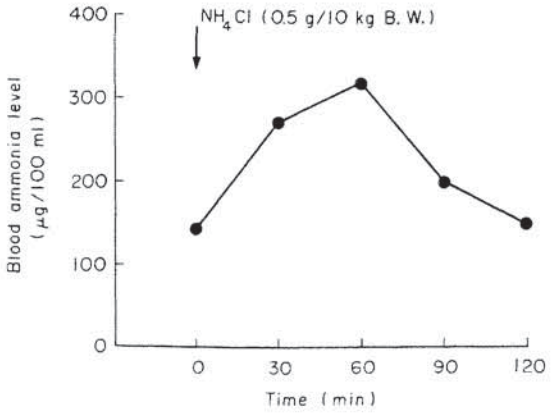

Fig. 3. Ammonia tolerance test.

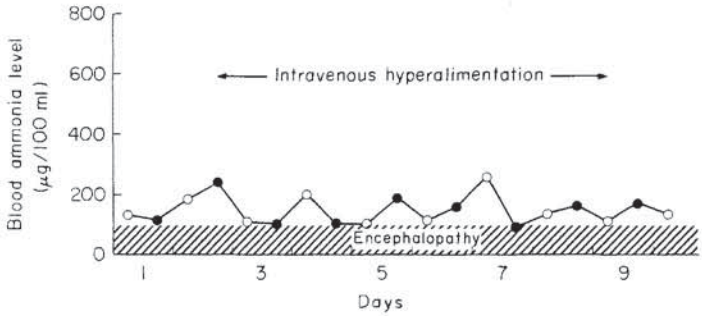

Fig. 4. Variation of blood ammonia levels in the stage of general liver failure. ○, levels at 9:00 a.m.; ●, levels at 8:00 p.m.

jaundice and ascites. He was not fed and was maintained with intravenous hyperalimentation. At this stage, regular diurnal fluctuation of blood ammonia characteristic of this patient was no longer seen (Fig. 4).

Variation of blood ammonia level in decompensated liver cirrhosis

In the following five cases, protein intake was restricted to less than 50 g a day. As a rule, blood ammonia was measured twice a day, 9:00 a.m. and 8:00 p.m. except Case 1.

A case of mesocaval shunt (*Case 1*). Blood ammonia measurement was done twelve times serially over two days. There was no regularity observed in the variation of the blood ammonia level (Fig. 5).

Cases of encephalopathy. In Case 2, the variation pattern was no longer diurnal but rather fluctuating with cycle of several days each. In Case 3, a trend of slight nocturnal rise of blood ammonia was seen before the onset of encephalopathy but the trend became unclear after the onset (Fig. 6).

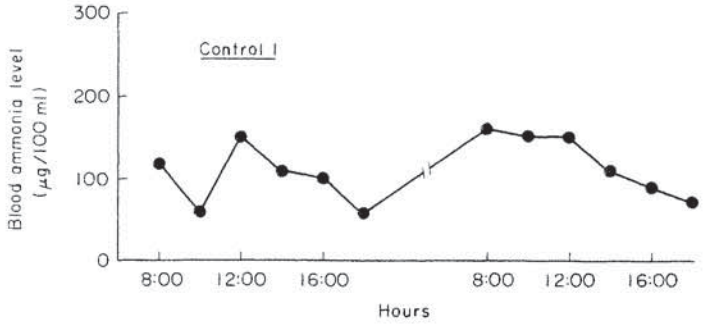

Fig. 5. Diurnal fluctuation of the blood ammonia levels in the cirrhotic patient with mesocaval anastomosis.

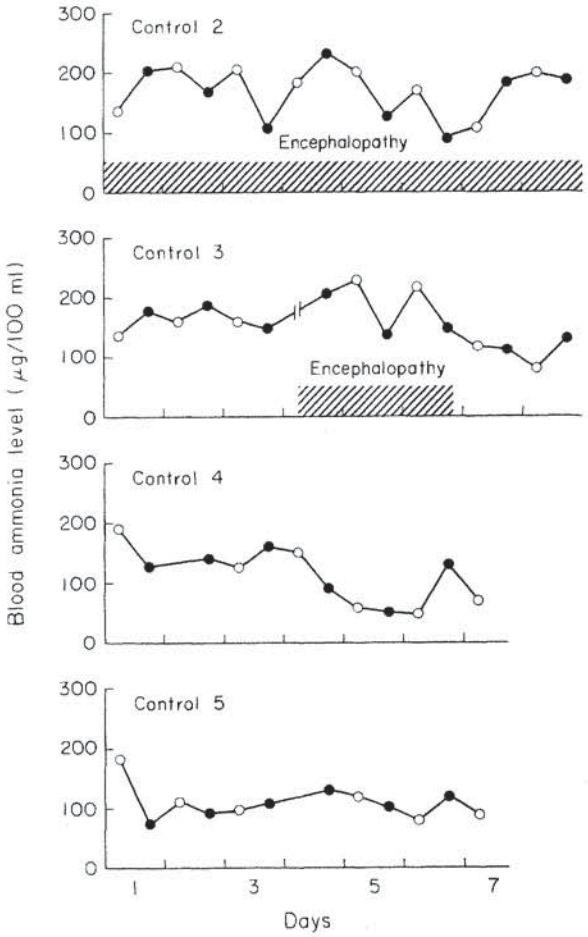

Fig. 6. Variation of the blood ammonia levels in decompensated cirrhotic cases. ○, levels at 9:00 a.m.; ●, levels at 8:00 p.m.

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