

A Case of Infectious Enterocolitis with Hyperammonemia

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Abstract : Case reports of hyperammonemia due to urease-producing bacteria are found occasionally, but most of them are associated with urinary tract infections. We experienced a case of infectious enterocolitis with hyperammonemia in which the causative bacteria was speculated to be urease-producing bacteria. A Japanese woman in her 70s had been diagnosed with microscopic polyangiitis in a nearby hospital and was transferred to our hospital. Although the microscopic polyangiitis was relatively under control after treatment with steroids and rituximab, frequent diarrhea with hyperammonemia (324 µg/dl) appeared and she became comatose. Her blood ammonia decreased to 47 µg/dl and her consciousness recovered to a normal state after antibiotic treatment for infectious enterocolitis and ammonia detoxification therapy. Liver dysfunction, portosystemic shunt, excessive protein intake and constipation were not observed, and she took no medications that would cause hyperammonemia. Although culture results could not identify urease-producing bacteria, considering the clinical course, acute hyperammonemia was suspected to be due to urease-producing bacteria infection. It is necessary to consider the influence of urease-producing bacteria as a cause of acute hyperammonemia not only in urinary tract infections but also in infective enterocolitis.

Keywords : hyperammonemia, urease, infectious enterocolitis.

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Introduction

Hyperammonemia often leads to disturbance of consciousness. Most of the causes of hyperammonemia are liver dysfunction. The influence of urease-producing bacteria is also one of the causes of hyperammonemia, but it is not frequent. There have been reports of hyperammonemia caused by urease-producing bacteria in urinary tract infections and empyema [1–5], but there are no reports of infectious enterocolitis. Here we report a case of infectious enterocolitis with hy-

perammonemia in which the causative bacterium was speculated to be urease-producing bacteria.

Case

A Japanese woman in her 70s was under medication for rheumatoid arthritis and atypical mycobacterial infection in a nearby hospital. She had a past history of surgery for osteoarthritis of the knee joint (49 years old) and right breast cancer (60 years old). She was admitted to a nearby general hospital with a fever and

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malaise one day in winter. Her laboratory data showed acute renal failure and positive myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), so she was diagnosed with microscopic polyangiitis. She was transferred to our hospital, and treatment with steroid therapy and rituximab was started. Although her microscopic polyangiitis was fairly well under control, frequent diarrhea was observed and inflammatory response increased from the 16th day of hospitalization. There was no improvement in her condition in spite of intravenous treatment of ceftriaxone, and on the 22nd day of hospitalization the patient became comatose. Her blood NH_3 concentration had raised to 324 $\mu\text{g}/\text{dl}$ and hemodialysis was performed, but there was no improvement in her consciousness, so she was admitted to the intensive care unit (ICU).

Her body temperature on admission to the ICU was 36.1°C. Her consciousness level was Eye opening 1 Verbal response 1 Motor response 4 (E1V1M4) in the Glasgow coma scale, her pupil size was 2.5 mm/2.5 mm (right/left), and her light reflex was normal. Although her hemodynamic state was stable, her tongue obstructed the airway and her S_pO_2 was 98% with an oxygen mask with reservoir (O_2 8 l/min). As the patient was comatose, we could not evaluate whether or not she had flapping tremor.

She was medicated with methylprednisolone, ceftriaxone, nifedipine, rabeprazole, azilsartan, sodium bicarbonate, erythromycin, and ramelteon on admission to the ICU.

The laboratory data on admission to the ICU are described in Table 1. Inflammatory response was increased as white blood cells: 30,800 $/\mu\text{l}$, C reactive protein: 2.71 mg/dl. Although renal dysfunction was observed as blood urea nitrogen: 93 mg/dl, creatinine: 3.95 mg/dl, there was no significant difference from at the time of hospitalization. Despite an increase in blood NH_3 concentration to 324 $\mu\text{g}/\text{dl}$, her liver function was relatively stable at the prothrombin time-international normalized ratio 1.21. Hemodialysis was performed before admission to the ICU, and the value of blood NH_3 had dropped to 226 $\mu\text{g}/\text{dl}$. Coronal section of abdominopelvic plain computed tomography image showed thickening of the ascending colon and ascites around the liver (Fig. 1A). Portosystemic shunts or liver atrophy was not clear. Head computed tomography

Table 1. Laboratory data on admission to the ICU

<Blood cell count>		<Blood chemistry>	
WBC	30800 $/\mu\text{l}$	TP	3.9 g/dl
RBC	3.83×10^6 $/\mu\text{l}$	Alb	1.9 g/dl
Hb	11.0 g/dl	T-Bil	0.6 mg/dl
Hct	31.8%	AST	20 IU/l
Plt	7.4×10^4 $/\mu\text{l}$	ALT	23 IU/l
		BUN	93 mg/dl
<Coagulation system>		Cre	3.95 mg/dl
PT	13.2 sec	Na	140 mEq/l
PT-INR	1.21	K	4.2 mEq/l
APTT	54.4 sec	Cl	104 mEq/l
Fib	145 mg/dl	Glu	171 mg/dl
FDP	12.0 $\mu\text{g}/\text{ml}$	CRP	2.71 mg/dl
AT-III	73%	PCT	1.12 ng/ml
<Atrial blood gas>		NH_3	324 $\mu\text{g}/\text{dl}$
pH	7.48		↓
pO_2	137.9 mmHg	(post HD)	226 $\mu\text{g}/\text{dl}$
pCO_2	25.4 mmHg		
HCO_3^-	19.1 mmol/l		
Lac	2.3 mmol/l		

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Hct: hematocrit, Plt: platelets, PT: prothrombin, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrin degradation products, AT-III: anti-thrombin III, Lac: lactate, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Glu: glucose, CRP: C reactive protein, PCT: procalcitonin, NH_3 : ammonia, HD: hemodialysis

showed cerebral edema (Fig. 1B). Her electroencephalography showed frequent triphasic waves.

She was diagnosed with hyperammonemic encephalopathy, and tracheal intubation was performed. Treatment with branched chain amino acid infusion, continuous hemodiafiltration and intravenous injection of meropenem were also started. Her blood NH_3 decreased to 47 $\mu\text{g}/\text{dl}$ and her consciousness recovered to a normal state on the third day after admission to the ICU. The tracheal tube was extubated on the fourth day and she left the ICU on the seventh day. Her head computed tomography after recovery of consciousness showed improvement of the cerebral edema (Fig. 1C). Inflammatory response also improved after administration of meropenem instead of ceftriaxone (Fig. 2). *Enterococcus* species and clostridium difficile toxin non-producing *Clostridium difficile* were isolated from her stool culture, and *Enterococcus faecium* was detected from one of the

aerobic bottles among two sets of blood culture bottles. *Enterococcus faecium* was considered to be contamination, as it was resistant to meropenem and could not explain her clinical course.

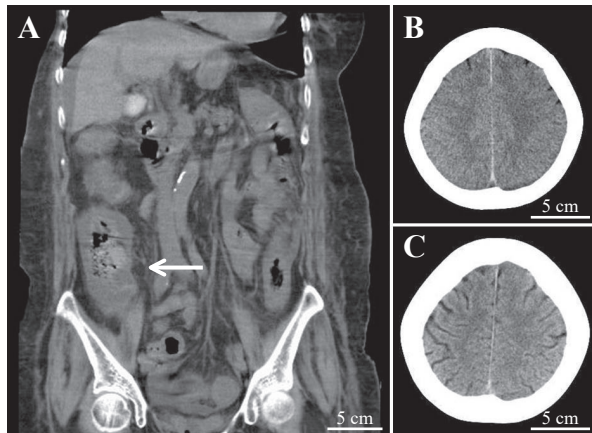


Fig. 1. Computed tomography images. A. A coronal section of abdominopelvic plain computed tomography image shows thickening of the ascending colon (white arrow) and ascites around the liver. B. A head computed tomography image on admission to the ICU shows cerebral edema. C. A head computed tomography image after recovery of consciousness shows improvement of cerebral edema.

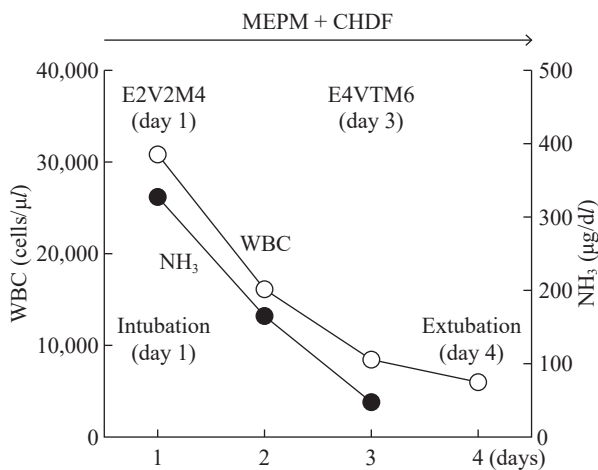


Fig. 2. Clinical course after admission to the ICU. Blood level of NH₃ decreased to 47 μ g/dl and consciousness was recovered on the third day. ●: NH₃, ○: WBC, E2V2M4: eye opening 2 verbal response 2 motor response 4, E4VTM6: eye opening 4 verbal response tube motor response 6, MEPM: meropenem, CHDF: continuous hemodiafiltration, WBC: white blood cells.

Discussion

The cause of the patient's comatose condition was considered to be hyperammonemic encephalopathy in this case, because her blood NH₃ was significantly high at 324 μ g/dl, her head computed tomography showed cerebral edema, and her consciousness and cerebral edema improved after NH₃ decreased to a normal range. Although the mechanism of cerebral edema in hepatic encephalopathy remains to be defined, it is well recognized that NH₃ is a major factor in its pathogenesis and that astrocyte swelling is a major component of cerebral edema [6].

There are three main causes of hyperammonemia: 1. metabolic disorders such as liver dysfunction and portosystemic shunts, 2. overproduction such as urease-producing bacteria infection, and 3. decreased excretion due to renal dysfunction or constipation [7–9]. Her liver function was relatively stable at the prothrombin time-international normalized ratio 1.21, and portal shunts or hepatic atrophy was not clear in CT. There was also no medical history of excessive protein intake or constipation during the clinical course. The influence of urease-producing bacteria and renal dysfunction were considered to be the causes of hyperammonemia in this case, but since renal dysfunction alone rarely causes hyperammonemia, the main cause of hyperammonemia was suspected to be infection with urease-producing bacteria. Hyperammonemia may occur due to the side effects of drugs such as valproic acid [10,11], but she was not medicated with any drugs that could cause hyperammonemia.

Urease is an enzyme that catalyzes hydrolysis of urea to ammonia and carbamate, and urease-producing bacteria have been reported to cause hyperammonemia in humans [7, 12]. Reports of hyperammonemia due to urease-producing bacteria such as *Klebsiella* spp., *Proteus* spp., *Corynebacterium* spp. and *Staphylococcus* spp. are commonly found, but most hyperammonemia are caused by urinary tract infections [1–4]. Besides urinary tract infections, there is a report of hyperammonemia due to empyema caused by anaerobic bacteria [5], but there are no reports of infectious enterocolitis. In cases of urinary tract infections and empyema, consciousness improved as blood NH₃ decreased to the normal range after intervention for treatment of infection, such as release of urinary retention, thoracic

drainage and administration of antibiotics. Neither urinary tract infection nor empyema was observed in this case, and the focus of inflammation was considered to be in the intestinal tract because of frequent diarrhea and edematous changes in the ascending colon.

Most of the blood ammonia of humans is derived from the intestinal tract in healthy condition. Although constipation was not observed in the present case, abdominal CT showed marked edema of the intestinal tract. Increased vascular permeability and inner pressure of the intestinal tract caused by enterocolitis might have affected the blood ammonia concentration. In cases of infectious enterocolitis, it might be possible that urease-producing bacteria abnormally proliferate and decompose urea to NH_3 in the intestinal tract, which leads to coma with hyperammonemia. Unlike urinary tract infections and empyema, it is usually difficult to identify accurate pathogenic bacteria in enterocolitis because there are various bacteria in the intestinal tract, which can explain why there have been no reports like this case so far.

Enterococcus species and *Clostridium difficile* were isolated from the feces, but neither of them are urease-producing bacteria. *Enterococcus faecium* was detected from the blood culture, but, as mentioned above, it was considered to be due to contamination. Colonies of *Enterococcus faecium* were applied to an urea agar base to confirm the urease productivity [13], but urease productivity was not confirmed.

When identifying pathogenic bacteria in infectious enterocolitis by culture methods, it is often difficult to identify the pathogenic bacteria, as mentioned above. Healthy adult gut microbiota are dominated by *Bacteroidetes* and *Firmicutes* but also include smaller proportions of *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* [14]. Among these, some *Bacteroides*, *Clostridium*, *Klebsiella*, *Proteus* and *Salmonella* have urease productivity. The bacterial flora of the intestinal tract in this case might have been disturbed due to steroids and immunosuppressive therapy. Intravenous ceftriaxone also might have been attributable to the abnormal proliferation of urease-producing anaerobic bacteria in the intestinal tract.

The cause of hyperammonemia was suspected to be urease-producing infection in this case, but it was not clear. We speculate that the bacterial flora in the

intestinal tract had been disturbed due to steroids, immunosuppressive therapy and ceftriaxone, and that urease-producing bacteria in the intestinal tract such as *Bacteroides*, *Clostridium*, *Klebsiella*, *Proteus* and *Salmonella* proliferated abnormally, developing into infectious enterocolitis with hyperammonemia.

Conclusions

We reported a case of infectious enterocolitis with hyperammonemia in which the causative bacteria was speculated to be urease-producing bacteria. It is necessary to consider the influence of urease-producing bacteria as a cause of hyperammonemia not only in urinary tract infections but also in infectious enterocolitis.

Conflicts of Interest

The authors declare no conflicts of interest.

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高アンモニア血症を伴った感染性腸炎の1例

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要 旨：ウレアーゼ産生菌のため高アンモニア血症を来した報告は散見されるが、その多くは尿路感染症である。今回我々はウレアーゼ産生菌による感染性腸炎のため高アンモニア血症を来したと考えられた症例を経験した。症例は70歳代女性。近医で顕微鏡的多発血管炎と診断され当院へ紹介となった。ステロイド療法およびリツキシマブを開始して顕微鏡的多発血管炎は比較的落ち着いていたが、頻回の下痢および高アンモニア血症(324 $\mu\text{g}/\text{d}$)を認め、昏睡状態となった。感染性腸炎および高アンモニア血症に対して、抗菌薬による加療およびアンモニアの解毒療法を開始したところ、血中アンモニアは47 $\mu\text{g}/\text{d}$ まで低下し意識は清明となった。高アンモニア血症の原因としては、肝機能障害や門脈体循環シャント、蛋白質過剰摂取、便秘は認めず、薬剤性の高アンモニア血症も否定的であり、ウレアーゼ産生菌によるアンモニア過剰産生が疑われた。本症例で提出した培養結果からはウレアーゼ産生能をもつ原因菌は特定できなかったが、培養で同定することが出来なかったウレアーゼ産生菌が、高アンモニア血症を引き起こしていた可能性が高いと考えられた。尿路感染症だけでなく、感染性腸炎においても、高アンモニア血症の原因としてウレアーゼ産生菌による影響を考慮する必要がある。

キーワード：高アンモニア血症, ウレアーゼ, 感染性腸炎.