A case of hyperammonemia due to urinary tract infection complicated by hypothyroidism

Hiroyuki Inoue 1, Takuro Nakada 1, Mizuho Namiki 2, Arino Yaguchi 2

ABSTRACT We report a case of disturbance of consciousness due to hyperammonemia stemming from urinary tract infection with urease-producing bacteria and complicated with hypothyroidism. An 84-year-old woman visited her family doctor with a history of excessive fatigue and was prescribed ciprofloxacin hydrochloride for cystitis and sulpiride for depression. The following day, she was brought to our hospital in an ambulance because of disturbance of consciousness. Sulpiride poisoning was suspected, and she was admitted to our emergency department. Because blood tests suggested hyperammonemia (197 µg/dl) and hypothyroidism, she was administered Lactulose, branched-chain amino acids, and thyroid hormones. Neither liver disease nor portosystemic shunting was observed in the blood or the imaging tests. The consciousness level initially improved along with the ammonia levels, however it later deteriorated again as the ammonia levels increased. Because urinary tract infection was complicated, we started administering antimicrobials. As a result, the level of ammonia normalized, and the level of consciousness improved. Arthrobacter cumminsii was detected by urine culture. Thus, we made a diagnosis as hyperammonemia due to urinary tract infection with urease-producing bacteria. In addition, hypothyroidism in the patient aggravated hyperammonemia. In cases of hyperammonemia unaccompanied by liver disease, urease-producing bacterial infection and/or hypothyroidism should be considered.

INTRODUCTION

While hyperammonemia causing a disturbance of consciousness often occurs as a complication of a liver dysfunction, it sometimes occurs as a complication of other diseases. In this paper, we report a disturbance of consciousness due to hyperammonemia caused by urinary tract infection with urease-producing bacteria, which is Corynebacterium pseudodiphtheriticum and exacerbated by hypothyroidism.

CASE REPORT

An 84-year-old woman was transferred to our emergency department because of disturbance of consciousness by an ambulance. She was treated for Graves’ disease in her 20’s, but the treatment has been discontinued. She regularly visited a family doctor for hypertension, hyperlipidemia, gastroesophageal reflux, and osteoporosis. Her regularly medications were: lansoprazole, metoclopramide, ethyl icosapentate, rosuvastatin calcium, mosapride citrate hydrate, magnesium hydroxide, alfalcacidol, risedronate sodium hydrate, meloxicam. One day before she came to our hospital, the patient visited her family doctor with complaining of lower abdominal pain, general fatigue, and low motivation. She received intravenous fluid for dehydration and was prescribed ciprofloxacin hydrochloride for diagnosis as cystitis. As she expressed suicidal ideation, sulpiride was administered for depression as well. On the following day, when the acquaintance visited the patient at home, the patient was...
found on the floor beside her bed, non-responsive. When the patient arrived at our hospital by an ambulance, her consciousness was Japan Coma Scale of 20, the blood pressure was 178/116 mmHg, the pulse rate was 80/min, the respiratory rate was 12/min, the body temperature was 35.6˚C, and the oxygen-saturation was 99% with a face mask oxygen at 5 L/min.

Physical examination revealed no abnormality except for the consciousness level.

Laboratory findings at the time of arrival at the hospital are shown in Table 1. Blood test detected a slightly high level of white blood cell counts and biochemical analyses found a slightly high level of LDH, BUN, and CK. Urine analysis detected protein, ketone bodies, and bacilluria. There was no abnormality revealed by plain chest x-ray, electrocardiogram, head CT, and head MRI. Because the cause of her disturbance of consciousness was not identified by initial examinations, the patient was admitted to the emergency department with primary diagnosis as sulpiride intoxication. Since the patient did not fully recover from unconsciousness on the 2nd day, other examinations were additionally performed. The additional examination findings on the 2nd day revealed hyperammonemia with 197 µg/dl and hypothyroidism with TSH 32.9 µU/ml, free T4 0.31 ng/dl and free T3 1.01pg/dl. Ultrasonography revealed an adenomatous goiter, however, no appreciable abnormality was found in the heart or abdomen. Since anti-thyperoxidasen (Anti-TPO) antibody (<0.3 U/ml) and anti-thyroglobulin (Anti-Tg) antibody (<0.3 U/ml) tests were negative, Hashimoto’s encephalopathy was not considered to be the cause of disturbance of consciousness, despite the laboratory evidence of hypothyroidism. Cerebrospinal fluid examinations denied the possibility of meningitis and encephalitis. Electroencephalography showed slow wave activity, but no appreciable abnormality consistent with epilepsy was detected. The hyperammonemia was considered as the possible cause of the disturbance of consciousness. Liver dysfunction or portosystemic shunting was not detected by the blood tests, and abdominal ultrasonography showed normal size liver with smooth margins. The echo structure of the liver was normal and CT revealed no liver deformity or no dilatation of the portal or inferior vena cava. Hyperammonemia was suspected as occurring from hypothyroidism. Lactulose, branched-chain amino acids, and thyroid hormones administration were started. Nevertheless any appreciable abnormalities in her electroencephalogram was not detected, phenytoin was also started because there was still a possibility that the patient was in nonconvulsive status epilepticus. Although the level of consciousness improved along with the ammonia level, we observed an aggravation of consciousness again on day 5 and day 6 as the level of ammonia started to rise again with 276 and 372 µg/dl, respectively. On day 6, cloudy urine was observed in the urinary catheter. Thus, we suspected an infection with obstructive uropathy and started to administer her 2g/day of ceftriaxone. As a result, the ammonia level became normal on day 7, and the level of consciousness improved.

### Table 1. Laboratory data on admission.

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP 7.6 g/dl</td>
<td>HbA1c 5.2 %</td>
</tr>
<tr>
<td>ALB 4.6 g/dl</td>
<td>TC 322 mg/dl</td>
</tr>
<tr>
<td>T.Bil 1.0 mg/dl</td>
<td>TG 74 mg/dl</td>
</tr>
<tr>
<td>AST 22 IU/l</td>
<td>LDL-C 236 mg/dl</td>
</tr>
<tr>
<td>ALT 12 IU/l</td>
<td>Ketone (3+)</td>
</tr>
<tr>
<td>LDH 281 IU/l</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>γGTP 37 IU/l</td>
<td>WBC 10,290 /µl</td>
</tr>
<tr>
<td>BUN 26.4 mg/dl</td>
<td>Hb 14.0 g/dl</td>
</tr>
<tr>
<td>Cre 0.73 mg/dl</td>
<td>Plt 18.7×10⁴ /µl</td>
</tr>
<tr>
<td>CK 195 IU/l</td>
<td>Coagulation</td>
</tr>
<tr>
<td>Na 141.7 mEq/l</td>
<td>PT 11.5 sec</td>
</tr>
<tr>
<td>K 3.4 mEq/l</td>
<td>APTT 26.0 sec</td>
</tr>
<tr>
<td>Cl 105 mEq/l</td>
<td>Infectious diseases assays</td>
</tr>
<tr>
<td>Ca 9.4 mg/dl</td>
<td>HBS Ag (-)</td>
</tr>
<tr>
<td>IP 2.8 mg/dl</td>
<td>HCV Ab (-)</td>
</tr>
<tr>
<td>BS 128 mg/dl</td>
<td></td>
</tr>
<tr>
<td>BS 128 mg/dl</td>
<td></td>
</tr>
</tbody>
</table>

Corynebacte-
Hiroyuki Inoue, et al

Corynebacterium pseudodiphtheriticum which was later identified as Arthrobacter cumminsii by gene analysis in the urine was detected by urine culture. After the discontinuation of ceftriaxone on day 12, neither the patient’s ammonia level nor the level of consciousness exacerbated. Since the patient had repeated cystitis before hospitalization, the bladder function test was performed at the department of urology and a hypotonic bladder and several bladder diverticuli were recognized. The patient was then treated with distigmine bromide and was discharged on day 36 without any complications.

DISCUSSION

In the present case, examination findings indicated that hyperammonemia was the cause of disturbance of consciousness, however it did not occur as a complication of a liver cirrhosis, hepatitis, and portosystemic shunting. The causes of hyperammonemia, other than liver diseases, are not common but some reports exist. In our patient, hyperammonemia was principally induced by production of ammonia in the urine with urease-producing bacteria. Because the urine gram stain revealed gram-positive bacilli and white blood cells and urine culture detected Corynebacterium pseudodiphtheriticum, which produced urease, that were considered to be responsible for the infection. The results of the urine examination also suggested that the urine of the patient was affected by the urease-producing bacteria and was alkaline with a pH of 8.5. In addition, urine retention in the hypotonic bladder combined with an increased production of ammonia. The mechanism of this condition is mentioned an increased production of ammonia in urine because of chronic urine retention and infection. Furthermore, urine retention causes an over-distention of bladder where ammonia in the urine is absorbed into the vesical venous plexus and because many of the veins surrounding the bladder drain into the inferior vena cava through the internal iliac vein, a large portion of absorbed ammonia is released directly into the systemic circulation, causing hyperammonemia. While there are existing reports on Corynebacterium urealyticum as the responsible bacteria for urinary tract infection, we could not find any literature on infection by Corynebacterium pseudodiphtheriticum. Therefore, we requested for a gene

---

Fig. 1. Clinical course of the patient.

Horizontal arrows show administrations of medications. Vertical arrows show interventions of bladder catheter.

[Graph showing the clinical course of the patient with error bars for each parameter over time, including serum ammonium (NH₃) (µg/dl), AST (IU/l), ALT (IU/l), WBC (×10³/µl), CRP (mg/dl), body temperature (BT) (˚C), and Glasgow coma scale (GCS).]

---

NH₃ (µg/dl) 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 (Day)

0 5 10 15

WBC (×10³/µl), CRP (mg/dl)

0 5 10 15 20

ALT (IU/l)

0 50 100 150 200

AST (IU/l), ALT (IU/l)

0 5 10 15

GCS

0 5 10 15

BT (˚C)

35.5 36.0 36.5 37.0 37.5 38.0

WBC (×10³/µl), CRP (mg/dl)

0 5 10 15 20

AST (IU/l), ALT (IU/l)

0 50 100 150 200

serum ammonium (NH₃) (µg/dl), AST (IU/l), ALT (IU/l), WBC (×10³/µl), CRP (mg/dl), body temperature (BT) (˚C).

Gray bar is a Glasgow coma scale (GCS),
Hyperammonemia due to UTI

Analysis. As a result, Corynebacterium pseudodiphtheriticum were identified as Arthrobacter cumminsii of Arthrobacter genus. Although Arthrobacter is a genus of urease-producing coryneform bacteria that commonly exist in soil, recent reports have indicated Arthrobacter species can exist in human bodies as well and cause infections. Some reports state that Arthrobacter cumminsii especially have a high isolation frequency in human samples and have caused urinary tract infections before, and this did not invalidate the idea that the bacteria caused the urinary tract infection in this case. Administration of ceftriaxone sodium and the insertion of a bladder catheter immediately decreased the ammonia levels and improved the patient’s consciousness. Therefore we concluded that hyperammonemia was mainly caused by production of urease by Arthrobacter cumminsii. Furthermore, it is known that thyroid hormones can affect liver function and structure, and some cases of hyperammonemia due to hypothyroidism have been reported. Despite the fact that the exact role of hypothyroidism in hyperammonemia is not clarified, several mechanisms have been proposed. Hypothyroidism aggravates the hyperammonemic state due to increased nitrogen load that decreases protein synthesis, increases protein catabolism and decreases intestinal motility promoting bacterial production of ammonia and augmenting its absorption. Moreover, hypothyroidism induces enzyme activity in the urea cycle leading to increased production of urea/ammonia. In addition, myopathy triggered by hypothyroidism may also increase ammonia production in the muscles, although thyroid myopathy was not obvious in this case. Some reports suggest that treatment of hypothyroidism can result in improvement of hyperammonemia. In our case, hypothyroidism was initially considered as a cause of hyperammonemia. Because hyperammonemia and consciousness improved after thyroid hormone replacement therapy on day 2 without antibiotics or a bladder catheter. However, hyperammonemia worsened accompanied with further disturbance of consciousness on day 6, despite continuing thyroid hormone replacement, lactulose, and branched-chain amino acids therapies. Hyperammonemia subsequently improved after antibiotics therapy and the insertion of a bladder catheter. Since the patient already had cystitis prior to hospitalization and antibiotics therapy had been discontinued until her recurrent hyperammonemia, we concluded that hyperammonemia causing disturbance of consciousness was fundamentally due to urinary tract infection, which was further exacerbated by hypothyroidism. When hyperammonemia occurs in cases with no evidence of liver disease or portosystemic shunting, the possibility of urinary tract infection due to urease-producing bacteria and hypothyroidism must be considered.

We reported this case at the 11th Japanese Association for Acute Medicine Chubu District meeting.

REFERENCES

甲状腺機能低下症を合併した尿路感染症による高アンモニア血症の1例

井上 博之1 中田 琠郎1 並木みずほ2 矢口 有乃2

要旨 甲状腺機能低下症を合併し、ウレアーゼ産生菌による尿路感染症から高アンモニア血症にて意識障害を来たした症例を経験したので報告する。症例は84歳の女性。入院前日に全身倦怠感を主訴に近医を受診し、膀胱炎の診断にて塩酸シプロフロキサシン、うつ状態にてスルピリドの内服が開始された。翌日、意識障害にて当院に救急搬送され、スルピリドによる中毒が疑われ入院となった。血液、画像検査では肝疾患や門脈-大循環シャントを認めなかったが、血液検査にて高アンモニア血症（197 μg/dl）および甲状腺機能低下症を認めため、ラクソース、分岐鎖アミノ酸製剤および甲状腺ホルモン剤を開始した。アンモニア値とともに意識レベルは改善傾向にあったが、再度アンモニア値が上昇し、意識レベルの悪化を認めた。膀胱カテーテル留置にて混濁した残尿を認め、抗菌薬を開始したところ、アンモニア値は正常化し、同時に意識レベルの改善を認めた。尿培養にてウレアーゼ産生のCorynebacterium pseudopseudodiphtheriticum（後述改善解析でArthrobacter cumminsiiと同定）が検出され、意識障害の原因としてウレアーゼ産生菌の尿路感染による高アンモニア血症が考えられた。また、甲状腺ホルモンがアンモニア代謝に影響を与えることが報告されており、増悪の一因と考えられた。肝疾患を伴わない高アンモニア血症では、ウレアーゼ産生菌の尿路感染症や甲状腺機能低下症も考慮する必要がある。

（日救急医会誌. 2012; 23: 398-402）

キーワード：意識障害、ウレアーゼ産生菌、アルスロバクター

原稿受理日：2011年11月8日（11-091）

1静岡赤十字病院救命救急センター・救急科 2東京女子医科大学救急医学