Teaching Point
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Hyperammonaemic encephalopathy and severe metabolic acidosis in a patient with chronic renal insufficiency years after ureterosigmoidostomy

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Introduction

We report a case of severe hyperchloraemic metabolic acidosis and hyperammonaemic encephalopathy in a patient with moderate renal insufficiency, who had discontinued oral bicarbonate administration. This patient had neither underlying liver disease nor urinary tract infection caused by urea-splitting bacteria. Bicarbonate administration resolved hyperchloraemic acidosis, but had no effect on hyperammonaemic encephalopathy. Hyperammonaemic encephalopathy resolved promptly after oral neomycin and lactulose. A review of acid-base, ammonia and nitrogen metabolism indicates that patients with moderate renal insufficiency are at high risk for metabolic disorders after ureterosigmoidostomy.

Case report

A 79-year-old male patient presented with somnolence, recurrent nausea and vomiting, constipation for several days and subsequently diarrhoea and hyperventilation. He complained about uneasiness a few days after he was discharged from a previous hospitalization with the consequence of a reduced food and fluid intake and failing to take his medication as prescribed.

During the previous hospitalization, the patient had received invasive cardiac diagnostics because of dyspnoea and angina pectoris during exertion. He had been diagnosed with a distal non-significant stenosis of the left main coronary artery (LMCA) developing into a significant stenosis in the proximal part of the left circumflexing artery (LCX). He had received angioplasty of the stenosis in the LCX and a stent had been successfully placed. The right coronary artery (RCA) had been occluded (already known from a previous coronary angiography). The patient had a chronic renal insufficiency stage 3 (K/DOQI criteria) and had received an ureterosigmoidostomy (Mainz pouch II) 8 years ago because of urothelial bladder carcinoma with radical extirpation of bladder and prostate.

On examination, the patient was somnolent and partially disoriented with slow response. His blood pressure, heart rate and temperature were normal. He was tachypnoeic with Kussmaul-type breathing. The chest was clear, the heart exhibited normal sounds without any murmurs. The abdomen was soft, bowel sounds were unremarkable. There was no peripheral acrœdema. Neurological findings besides somnolence and disorientation included a stiffness of the neck (albeit no sign of meningism), flapping tremor; other neurological deficits were not detected. The emergency department’s blood gas analyser provided the initial information: pH 7.036, pCO2 22.3 mmHg, pHCO3 5.7 mmHg, Anion Gap 11.9, Na 142 mmol/l, K 5.2 mmol/l, haemoglobin 10.2 g/dl, glucose 130 mg/dl, lactate 6 mg/dl (Table 1). A chest X-ray revealed no pathological findings. More laboratory data was obtained: C-reactive protein (CRP) 0.66 mg/dl, creatinine 3.03 mg/dl, total protein 7.2 g/dl, AST 16 U/l, creatinine kinase 30 (U/l). Leucocyte, erythrocyte and thromboocyte counts were normal. He had hyperammonaemia (131 µmol/l; normal range 10–50 µmol/l)
The patient's medication was modified to include the administration of lactulose and neomycin are denoted by arrows. Without any elevation of liver enzymes, INR and prothrombin time were normal. The patient received bicarbonate infusions intravenously; however, he did not improve clinically despite improvement of his metabolic acidosis (day 1 + 2 h; Table 1, Figure 1). Administration of potassium was not required. Oral neomycin and lactulose were given to suppress faecal urease activity and ammonia production by bowel flora. The patient responded promptly to this therapy; the encephalopathy resolved clinically on day 3. Ammonia levels were normal. The acidosis was nearly corrected after continued intravenous administration of bicarbonate solution on day 3 (Table 1, Figure 1). An abdominal ultrasound showed trapped air within the left kidney. A computed tomography (CT) scan of the abdomen confirmed these findings (Figure 3). Flatulence was suspected, since CRP, leucocyte count and body temperature were normal. The patient's medication was modified to include the daily oral administration of 6 g of bicarbonate. Since the acid-base disturbance was under control and since the patient had improved markedly, he was discharged and referred to his ambulatory nephrologist.

One of the authors has seen the patient 1 year later. The patient was doing well on oral therapy with 8 g of bicarbonate per day. He had no oedema and did not require haemodialysis. His pH was 7.36, pCO2 40.2 mmol/l, HCO3- 22.5 mmol/l, Cl- 110 mmol/l. His creatinine was 1.8 mg/dl. He had no signs of hyperammonaemic encephalopathy.

### Questions and discussion

Ureterosigmoidostomy can be complicated by pyelonephritis, renal calculi, hyperchloraemic acidosis and colonic neoplasia. Much of the investigation of the metabolic consequences of urinary diversion and their follow-up has been conducted by European urologists [1]. Since the decline in renal function is moderate in patients with ureterosigmoidostomy, nephrologists see those patients relatively late, i.e. usually years after the surgery when kidney function is impaired. At this stage, metabolic disturbances might be severe and complex. Establishing the underlying cause is vital in planning definitive procedures to reverse causative factors and in preventing further episodes.

**What kind of acidosis did our patient have?**

**Should the acidosis be treated?**

Acid–base disorders seldom kill. However, the mechanisms and associated complications certainly do. Acid–base problems, especially metabolic acidosis, are serious complications in patients with urinary diversion such as a Mainz Pouch II; 80% of the patients with urinary diversion receive oral bicarbonate/citrate [2,3]. The type of acid–base disturbances in our patient was easily determined following a stepwise approach [4]: A high [H+] (i.e. a low pH) and a low [HCO3-] defined metabolic acidosis.

To determine whether the metabolic acidosis is simple or mixed, the expected compensatory response of the lungs has to be appreciated. The millimol/litre decrease in plasma [HCO3-] should approximately equal the millimetres of mercury decrease in pCO2 if the acidosis is compensated correctly. In our patient, the estimated pCO2 was pCO2 = 1.5 × [HCO3-] + 8 = 19.0 mmHg. This value approximately equated the measured pCO2 of 22 mmHg indicating a simple and correctly compensated metabolic acidosis. To elucidate whether acid gain or bicarbonate loss is responsible for the metabolic acidosis, the calculation of the anion gap (AG) was estimated [5]. The AG is the difference between the plasma major cation (Na+) and the major anion (Cl- + HCO3-) concentrations, or equal to the difference between unmeasured anions and unmeasured cations. An increased AG metabolic acidosis is frequently a result of an increase in unmeasured anions caused by acid gain due to metabolic disturbances (ketoacidosis, lactic acidosis, renal failure or ingestion of e.g. methanol, ethylene glycol and salicylates). Bicarbonate loss does not disturb the AG. Since in our patient the AG was not

### Table 1. Laboratory results (blood gas analyses, BGA): the results represent the patient’s acid-base status before (day 1), at day 1 + 2 h and at day 3 after intravenous bicarbonate infusions. AG, anion gap

<table>
<thead>
<tr>
<th>BGA</th>
<th>Day 1</th>
<th>Day 1 + 2 h</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.036</td>
<td>7.241</td>
<td>7.384</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>22.3</td>
<td>23.4</td>
<td>33.8</td>
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<tr>
<td>[HCO3-] (mmHg)</td>
<td>5.7</td>
<td>9.7</td>
<td>19.7</td>
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<tr>
<td>AG</td>
<td>11.9</td>
<td>10.8</td>
<td>12.9</td>
</tr>
<tr>
<td>Na (mmol/l)</td>
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<td>149</td>
<td>140</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>5.1</td>
<td>4.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Cl (mmol/l)</td>
<td>124</td>
<td>123</td>
<td>109</td>
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</tbody>
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![Fig. 1.](image-url)
elevated (Table 1), the reason for the metabolic acidosis had to be a loss of NaHCO₃. This loss can occur either through the kidneys or via the gastrointestinal (GI) tract. Renal loss occurs due to disturbances in the tubular transport (renal tubular acidosis) whereas GI loss can be caused by diarrhoea, pancreatico-cutaneous fistula, biliary drainage and can occur after ureterosigmoidostomy [6]. In order to distinguish between these two conditions, the urine net charge (UAG) can be estimated. It equals the sum of the major measured cations minus the major anions (UAG=[Na⁺]+[K⁺]−[Cl⁻]) or, in analogy to the plasma AG, the UAG is the difference between unmeasured anions and unmeasured cations. The major unmeasured cation in the urine is the ammonium ion (NH₄⁺); its renal excretion is a physiological response to the daily acid load and is increased substantially during metabolic acidosis. When NaHCO₃ is lost via the GI tract, the generation of NH₄⁺ should increase, and the calculated UAG should be negative. On the other hand, when NaHCO₃ is lost via the kidneys or the kidneys are unable to generate sufficient amounts of NH₄⁺, the UAG is positive. In our patient, estimation of UAG is not helpful because the urine is contaminated with the faeces due to ureterosigmoidostomy.

Hyperchloraemic metabolic acidosis is present in >50% of the patients with ureterosigmoidostomy [7] and can be viewed as the main metabolic disorder in urinary diversion with the mixture of faeces and urine; a price to be paid in continent urinary diversion. Hyperchloraemic metabolic acidosis requires absorption of chloride ions from the urine via the colonic wall in exchange for bicarbonate (Figure 2). However, the development of the acidosis is not primarily driven by the colonic chloride [8]. Instead, hyperchloraemia is secondary due to bicarbonate loss and is based on insufficient bicarbonate substitution (Figure 2). The present patient had a severe hyperchloraemic metabolic acidosis induced by failure to take the alkalinizing medication as prescribed. Due to recurrent vomiting and reduced food and fluid intake the pre-existing chronic renal insufficiency may have worsened followed by a reduced ammonium excretion leading to accumulation of acids. Unfortunately, we were not able to determine the UAG to estimate the quantitative contribution of the latter component. Nevertheless, regular bicarbonate or sodium citrate intake is required to prevent hyperchloraemic acidosis by intestinal bicarbonate loss in patients with ureterosigmoidostomy. Patients with renal insufficiency have reduced capabilities for renal compensation of this acidosis, and thus are especially endangered.

Why did the patient develop hyperammonaemic encephalopathy?

In 1852, Mr Simon from St Thomas’ hospital in London demonstrated the first urinary diversion via the rectum in a 13-year-old boy suffering from exstrophy of the bladder. In the post-operative course, the boy suffered from recurrent fever. After temporary improvement, he died about 12 months after the operation. Hyperammonaemic encephalopathy has been reported in patients with ureterosigmoidostomy [7,9–12]. This complication was recognized as early as measurements of plasma ammonia levels became available to clinicians. It is believed that this condition is rare; however, the exact incidence is unknown. The long-term effects of ureterosigmoidostomy on cognitive function are also unknown. Mr Simon’s patient ‘died of debility and low peritonitis’; measurements of ammonia were not available to him.

Hyperammonaemic encephalopathy most often occurs in the context of liver disease [13]. The diagnosis is straightforward because of accompanying laboratory and clinical signs of liver insufficiency. Accordingly, hyperammonaemic coma in ureterosigmoidostomy has been associated with acute and chronic liver failure [14–19]. Our patient exhibited neither clinical signs nor laboratory results suggesting liver dysfunction.

Therefore, we concluded that the present hyperammonaemia was of non-hepatic origin. Amino acids, the products of endogenous and exogenous protein degradation, are metabolized by hepatic transamination and oxidative deamination to produce ammonia. Ammonia is subsequently converted to urea and excreted by the kidneys. Any disruption of this cycle of nitrogen excretion has the potential to cause hyperammonaemia and encephalopathy (Figure 2). First, the cycle may not be able to handle a normal nitrogen load. Genetic disorders of the urea cycle, for example, such as carbamoylphosphate synthetase I deficiency (CPIS), ornithine transcarbamylase deficiency (OTC), arginosuccinic acid synthetase deficiency (ASS), arginosuccinic acid lysase deficiency (ASL) or arginase deficiency (ARG) may cause hyperammonaemia and encephalopathy [20]. In our patient, this cause seems to be unlikely. Second, the nitrogen load may bypass the liver, entering directly into the systemic circulation via portosystemic shunts. Third, though liver function is normal, excess nitrogen may over-saturate the liver’s excretory capacity.

In patients with Mainz Pouch II (ureterosigmoidostomy), the urine is excreted directly into the sigmoid colon and finally excreted with the faeces. In this condition, there is colonic absorption of ammonia to the portal circulation. However, ammonia absorbed in the colon can bypass the portal circulation via portosystemic shunts, which itself can cause hyperammonaemic encephalopathy [13]. Ammonia absorbed in the rectum will also bypass the portal circulation because rectal veins are connected with the internal iliac veins. Therefore, patients with ureterosigmoidostomy are at high risk for hyperammonaemia. Increased production of ammonia, sufficient to over-saturate hepatic excretory pathways after direct diffusion of ammonia into the inferior vena cava bypassing the liver,
Fig. 2. Schematic overview of the major sources of ammonia production and its excretion in ureterosigmoidostomy and possible causes of non-hepatic hyperammonaemia (modified from [13,51]). The inset shows a cellular model for bicarbonate secretion in colonic epithelial cells: HCO$_3^-$ is secreted by different mechanisms, including electronegic secretion via luminal CFTR Cl$^-$/HCO$_3^-$ exchanger, a luminal SCFA$^-$/HCO$_3^-$ exchanger, and the luminal Cl$^-$/HCO$_3^-$ exchanger DRA. CFTR may also serve as recycling pathway for Cl$^-$, which has been taken up by the luminal Cl$^-$/HCO$_3^-$ exchanger DRA or basolateral Na$^+$-coupled HCO$_3^-$ transporter. Electroneutral secretion of HCO$_3^-$ is paralleled by the activity of the Na$^+$/$H^+$ exchanger NHE3 or NHE2. K$^+$ recycles via basolateral K$^+$ channels, and Cl$^-$ is transported to the blood side via basolateral KCC1 (K$^-$-Cl cotransporter) and probably Cl$^-$ channels. CFTR, cystic fibrosis transmembrane conductance regulator; SCFA, short chain fatty acid; DRA, ‘downregulated in adenoma’, a luminal Cl$^-$/HCO$_3^-$ exchanger.
urinary NH and mucosa and colonic absorption of ammonia and because the contact time of urine with the colonic transit. This delayed transit is potentially dangerous diarrhoea, we also expected a period of delayed colonic transit. Due to the reduced amount of faeces in the colon after bowel, and the action of urea-splitting bacteria in the colon alone (bacterial ammonioponies) [9,10,22] have been described in several case reports and have all been proposed as possible mechanisms to explain hyperammonaemic encephalopathy after urinary diversion. Over-saturation of hepatic excretory pathways is aggravated by renal insufficiency. This has been demonstrated in rats with ureterocolostomy and chronic renal failure induced by subtotal nephrectomy [23].

Our patient reported constipation and subsequently diarrhoea. The diarrhoea was severe according to the acid–base disturbance. Increased production of ammonia in the colon from urea-splitting bacteria and subsequent absorption of ammonia was suspected. Due to the reduced amount of faeces in the colon after diarrhoea, we also expected a period of delayed colonic transit. This delayed transit is potentially dangerous because the contact time of urine with the colonic mucosa and colonic absorption of ammonia and urinary NH\textsuperscript{+} (which is actually a mixture of urine and faeces) will increase. Accordingly, hyperammonaemic encephalopathy induced by coprostasis has been reported in ureterosigmoidostomy [9]. The alkaline pH in the colon and rectum is expected to sustain a high luminal ratio of NH\textsubscript{3}/NH\textsubscript{4}\textsuperscript{+}, which will aggravate the situation. Moderate renal insufficiency will serve as additional factor of excess nitrogen to over-saturate the liver’s excretory capacity. All these conditions were present in our patient. Other possible causes such as gastrointestinal bleeding [13], drug administration (e.g. valproate [24]), and haematological disorders such as lymphomas ([25–27]) were unlikely because of the laboratory findings and medical history.

We administered oral neomycin and lactulose to suppress faecal urease activity and ammonia production by bowel flora and to stimulate defaecation [28,29]. The patient responded promptly to this therapy; he had 4–5 defecations per day and his encephalopathy resolved clinically on day 3. Ammonia levels returned to normal values. Haemodialysis was not necessary to manage this case of over-saturation of the liver’s excretory capacity by excess nitrogen.

Intrarenal emphysema

Initially, we were surprised by an abdominal ultrasound, which suspected intrarenal emphysema. This differential diagnosis was confirmed by a CT scan of the abdomen (Figure 3). Hyperammonaemic encephalopathy can develop in patients with ureterosigmoidostomy as a result of urea-splitting urinary tract infections [10,27,30,31]. Either the gas or the gas-producing bacteria themselves can ascend through the ureter into the kidneys. A severe form is the emphysematous pyelonephritis, first described in 1962 [32]. It is characterized by a necrotizing mostly unilateral renal infection and can induce gangrenous destruction and sepsis. This life-threatening condition may require urgent nephrectomy [33,34]. It can be caused by bacteria (Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Aerobacter aerogenes, Citrobacter, Campylobacter; some of them urea-splitting bacteria) and in rare occasions by fungi (Candida species [35]). However, we hypothesized that flatulence was the cause for the air inclusions in the kidney in our patient, since CRP, leucocyte count and body temperature were normal. Neither bacteria nor Candida species nor Aspergillus species could be cultivated in blood samples. In conclusion, our patient had no emphysematous pyelonephritis.

To summarize, in the present patient with renal impairment, ureterosigmoidostomy (Mainz Pouch II) was complicated by two severe complications. The patient presented with hyperchloraemic metabolic acidosis and hyperammonaemic encephalopathy. The metabolic acidosis was caused by severe bicarbonate loss through the lower GI tract and discontinuation of oral bicarbonate administration. The hyperammonaemic encephalopathy was most likely non-hepatic and caused by a combination of different factors, including increased ammonia production by urea-splitting bacteria in the colon, prolonged transit of urine in the colon (which is associated with long contact time of NH\textsubscript{3}/NH\textsubscript{4}\textsuperscript{+} with the colon mucosa), reduced fluid intake followed by a deterioration of renal function (azotaemia) with reduced ammonium excretion and elevation of systemic nitrogen, which all led to over-saturation of the liver’s excretory capacity by excess nitrogen. Ureagenesis in the liver consumes up to 1000 mmol/day of bicarbonate in humans as a result of
$2\text{NH}_4^+ + 2\text{HCO}_3^- \rightarrow \text{urea} + \text{CO}_2 + 3\text{H}_2\text{O}$. Although a case of hyperammonaemia in chronic renal failure has been reported to be successfully treated with the infusion of NaHCO$_3$ [36], a significant role of the liver in the regulation of acid–base balance could not be demonstrated [37–40]. Furthermore, results on rats have shown that ureagenesis in the liver is not directly affected by acid–base status, but depends on the amount of nitrogenous waste to be metabolized in the liver [41].

To our knowledge, this is the first report of both, severe hyperchloraemic metabolic acidosis and hyperammonaemic encephalopathy after ureterosigmoidostomy (Mainz Pouch II). Clearly, our patient’s moderate renal insufficiency made the clinical picture more dramatic and more complicated.

**Diagnosis**

(i) Metabolic acidosis caused by severe bicarbonate loss through the lower GI tract and discontinuation of oral bicarbonate administration.

(ii) Non-hepatic hyperammonaemic encephalopathy, probably by over-saturation of the liver’s excretory capacity by excess nitrogenous waste.

**Teaching points**

(i) Patients with ureterosigmoidostomy need regular bicarbonate intake, especially in chronic renal disease. Daily oral administration of 8 g of sodium bicarbonate are not unusual to compensate for bicarbonate loss through the lower gastrointestinal tract. Sodium bicarbonate of 8 g (containing only 2.3 g or 96 mmol of sodium) may have only a small impact on the extracellular (sodium) volume homeostasis, because the typical Western diet contains $\sim$150 mmol sodium per day.

(ii) Correction of the acidosis without potassium replacement might be dangerous. Hypokalaemia has been described as possible life-threatening complication after ureterosigmoidostomy [42–49].

(iii) Coprostasis should be avoided in patients after ureterosigmoidostomy, especially in immobilized patients (e.g. after cardiac catheterization).

(iv) Hyperammonaemic encephalopathy can be a life-threatening complication of ureterosigmoidostomy. It will never come to our knowledge whether Mr Simon’s patient developed debility due to this complication.

(v) Consider neomycin and lactulose when non-hepatic hyperammonaemia or urea-splitting bacteria in the colon are suspected. Consider protein-restricted diet and haemodialysis to reduce urea and ammonia if necessary [20,50].

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**Conflict of interest statement.** None declared.

**References**


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