CASE REPORT

Delayed Onset of Central Pontine Myelinolysis: A Rare Presentation Following Surgery for Severe Acute Necrotic Pancreatitis Complicating Infection

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ABSTRACT

Introduction Central pontine myelinolysis (CPM) is a rare osmotic demyelination syndrome. Myelinolysis following patients with acute pancreatitis (AP) is extremely rare. To the best of our knowledge, only two cases have been reported in prior literatures. However, the associated mechanisms on patients with CPM secondary to AP have remained unclear. **Patient concerns** (1) A 58-year-old woman, with upper abdomen pain complicating nausea and vomiting for ten days, had a fever and abdominal pain (first hospitalization). (2) On second hospitalization, she suffered from abdominal pain and distension. (3) On third hospitalization, she was admitted because of "intense diarrhea for two days and drowsiness for half a day". On the eighth day, the patient deteriorated with onset of anisocoria. On the 12th day, patient's mental status became conscious, as well as a new-onset mutism. **Diagnosis** (1) Contrast-enhanced CT revealed a severe acute necrotic pancreatitis (first hospitalization). (2) On second hospitalization, laboratory tests showed glucose of 12.3 mmol/L and a hyponatremia of 125.9 mmol/L. Follow-up CT showed the presence of abdominal infection. (3) On third hospitalization, laboratory findings included a hypokalemia of 2.4 mmol/L, a severe hypernatremia of 192 mmol/L and a severe hyperchloremia of 150 mmol/L, and a creatinine of 118.7umol/L. Brain MRI, performed 4.5 months after AP onset, revealed the central pontine myelinolysis. **Interventions** (1) She received intravenous fluids and insulin treatment, initiated electrolyte corrections, and anti-infection (first hospitalization). (2) On second hospitalization, the operation including pancreatic abscess removal and cholecystectomy was performed on 2.5 months after AP onset. (3) As for third hospitalization, she received potassium and fluid infusions, diuresis, and continuous renal replacement therapy. Electrolyte corrections were continuously proceeded. **Outcome** When she was discharged from third hospitalization, the patient was in unconsciousness with a lethargy status. By means of telephone follow-up, the patient died five days after the third discharge. **Conclusion** It is important to make the early diagnosis of CPM in AP patients (especially severe necrotic pancreatitis) if severe electrolyte disturbance and subsequently altered mental status or transient anisocoria occur. Based on highly specific imaging findings, MRI should be performed in time when delayed onset of CPM following AP is suspected.

INTRODUCTION

Central pontine myelinolysis (CPM) is a rare osmotic demyelination syndrome [1]. Clinically, a majority of patients with CPM have a highly severe prognosis. In those cases, symmetrical myelin sheaths' disruption was detected in white matter areas containing heavily myelinated fibers, particularly in pons [1, 2, 3, 4]. Currently, there were a few CPM cases with osmolarity disorder described predominantly in alcoholic and malnourished patients [1, 2, 3, 4]. However, myelinolysis following patients with acute pancreatitis (AP) is extremely rare. To data, the associated mechanisms on patients with CPM secondary to AP have remained unclear. We herein report a case of delayed onset of CPM in a female patient (without alcoholism) who underwent two operations for severe acute necrotic pancreatitis complicating infection, in the setting of severe electrolyte disturbance, which demonstrates the importance of making this diagnosis to AP patients presenting with diarrhea, drowsiness, transient anisocoria and delayed onset speechless (mutism).

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Abbreviations AP acute pancreatitis; APACHE Acute Physiology and Chronic Health Evaluation; CPM central pontine myelinolysis; CT computed tomography; CRRT continuous renal replacement therapy; ICU intensive care unit; MRI magnetic resonance imaging
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CASE REPORT

First Hospitalization

A fifty-eighty-year-old woman, with upper abdomen pain complicating nausea and vomiting for ten days, was medicated with symptomatic treatment and a subsequent

laparoscopic exploratory laparotomy due to no profound pain relief, and developed critically ill in the patient's local hospital. Then, she was transferred to our hospital as an emergency case. Upon admission, she had a fever (39.3°C), abdominal pain and four abdominal drainage tubes, and her neurological physical examination was unremarkable. Laboratory tests after admission showed a neutrophils value of 8.2×10^9/L, a hemoglobin of 141 g/L, a blood amylase of 1344 U/L, a blood lipase of 1334 U/L, a glucose of 12.3 mmol/L, a hyperchloremia of 118 mmol/L and a hypocalcemia of 2 mmol/L. Contrast-enhanced abdominal computed tomography (CT) after admission revealed findings of a severe necrotic pancreatitis **(Figure 1)**. She was admitted to the intensive care unit (ICU) and received antimicrobial enzymes, intravenous fluids and regular insulin treatment, initiated electrolyte corrections, and anti-infection therapy. The Acute Physiology and Chronic Health Evaluation (APACHE) II score at 48 hours after admission for her was 11 points. On the third day after admission, percutaneous cholecystocentesis was performed because of massively enlarged gall bladder **(Figure 1)**. Active treatment including careful correction of electrolyte disturbances was performed in the following days, but she was still in a series of electrolyte imbalances **(Figure 2)**. During 63 days of hospital stay, the patient had a symptomatic improvement and then she was discharged with a normal mental status.

Second Hospitalization

Time intervals between first discharge from our hospital and second admission were only two days. On this admission, she was alert, and suffered from abdominal pain and distension. Laboratory tests after admission showed a neutrophils value of 10.9×10^9/L, glucose of 12.3 mmol/L and a conspicuous hyponatremia of 125.9 mmol/L. After 13 days of regular insulin and electrolyte corrections, the patient had a persistent fever (up to 39.2°C). Follow-up CT, performed two months after the acute event, showed pancreatic collections with a gas-bubble sign, indicating the presence of abdominal infection **(Figure 1)**. In addition, abdominal drainage fluid culture represented the infection of acinetobacter baumannii (multiple resistant bacteria). Consequently, the second operation including pancreatic abscess removal and catheterization, cholecystectomy and jejunostomy was performed on 2.5 months after AP onset. After surgery, the patient was transferred to ICU for intensive care. Laboratory tests showed a neutrophils value of 7.5×10^9/L, a hemoglobin of 76 g/L, and a hyponatremia of 134.7mmol/L. Subsequently, plasma, balance fluid and saline infusions and anti-infective therapy were proceeded. Some improvements were seen in the following days. On the 28th day, the patient volunteered to be discharged, kept a normal neurological mental status, but presented a slight hypernatremia of 148.6 mmol/L and a hyperchloremia of 116.8 mmol/L before her discharge **(Figure 2)** despite careful electrolyte corrections.

Third Hospitalization

Time intervals between second discharge and third admission were only three days. She was admitted to our emergency department because of "intense diarrhea (6-7 times per day) for two days and drowsiness for half

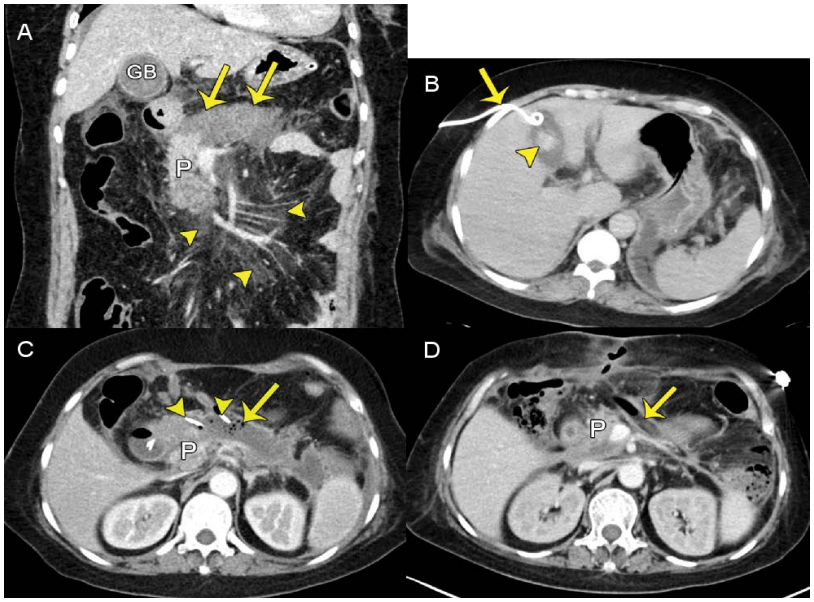

Figure 1. (a). First hospitalization. Contrast-enhanced computed tomography (CT) after admission readily show a large amount of nonenhanced areas (arrows) in the body and tail of the pancreas, compatible with parenchyma necrosis. The extent of necrosis is nearly 50% of the pancreas. Extrapancreatic spread is also seen (arrowheads). **(b).** On the third day after admission, percutaneous cholecystocentesis was performed. High density drainage tube (arrow) and a gallstone are demonstrated on CT. **(c).** Second hospitalization. Follow-up CT, performed 2 months after the acute event, shows pancreatic collections admixed with small quantities of gas-bubble (arrow), indicating the presence of abdominal infection. Note high density drainage tubes (arrowheads) are set by the first laparoscopic exploratory in the patient's local hospital. **(d).** Third hospitalization. Follow-up CT before the third discharge shows that peripancreatic effusion is almost completely absorbed. Note the abdominal drainage tube (arrow).
GB gallbladder; P pancreas

a day". On admission, the patient was mentally lethargic. Physical examinations showed her temperature of 38.1°C, the pulse of 68/minute, breathing of 21/minute, and blood pressure of 109/59 mmHg. Laboratory findings after admission included a hypokalemia of 2.4 mmol/L, a severe hypernatremia of 192 mmol/L and a severe hyperchloremia of 150 mmol/L, as well as a glucose of 15.2 mmol/L, an urea nitrogen of 14.3 mmol/L and a creatinine of 118.7umol/L. Then, she received potassium and crystal fluid infusions, diuresis treatment and an insulin pump to control blood sugar in ICU. During one day of electrolyte corrections, she additionally underwent hemodialysis treatment, as continuous renal replacement therapy (CRRT) of 400 ml per hour. By the seventh day, serum sodium and chlorine levels had returned to normal, along with normal daily urine volume, leading to withdrawal of CRRT. As shown in **Figure 1**, serum sodium and chlorine levels developed fluctuant in the following days despite continuous electrolyte corrections. On the eighth day, the patient deteriorated with onset of anisocoria in both pupils (left pupil of 4 mm and right pupil of 2 mm). Emergency head CT scan was performed and acute cerebral hemorrhage was excluded. On the nineth day, the anisocoria had returned to normal. On the 12th day, the patient's mental status became consciousand showed a new-onset speechless (mutism). Subsequent brain magnetic resonance imaging (MRI) performed 4.5 months after the acute event, revealed almost symmetric T1-weighted hypointense and T2-weighted hyperintense pontine lesions, along with involvement spread to midbrain **(Figure 3)**. The MRI findings were suggestive of central pontine myelinolysis. And then electrolyte corrections were proceeded. Unfortunately, the patient's family needed her to be discharged one day later after the final diagnosis. Follow-up CT before her discharge showed that peripancreatic collections were almost completely absorbed **(Figure 1)**. When she was discharged, serum sodium and chlorine levels returned to normal but the patient was in unconsciousness with a lethargy status. By means of telephone follow-up, the patient died five days later after final discharge.

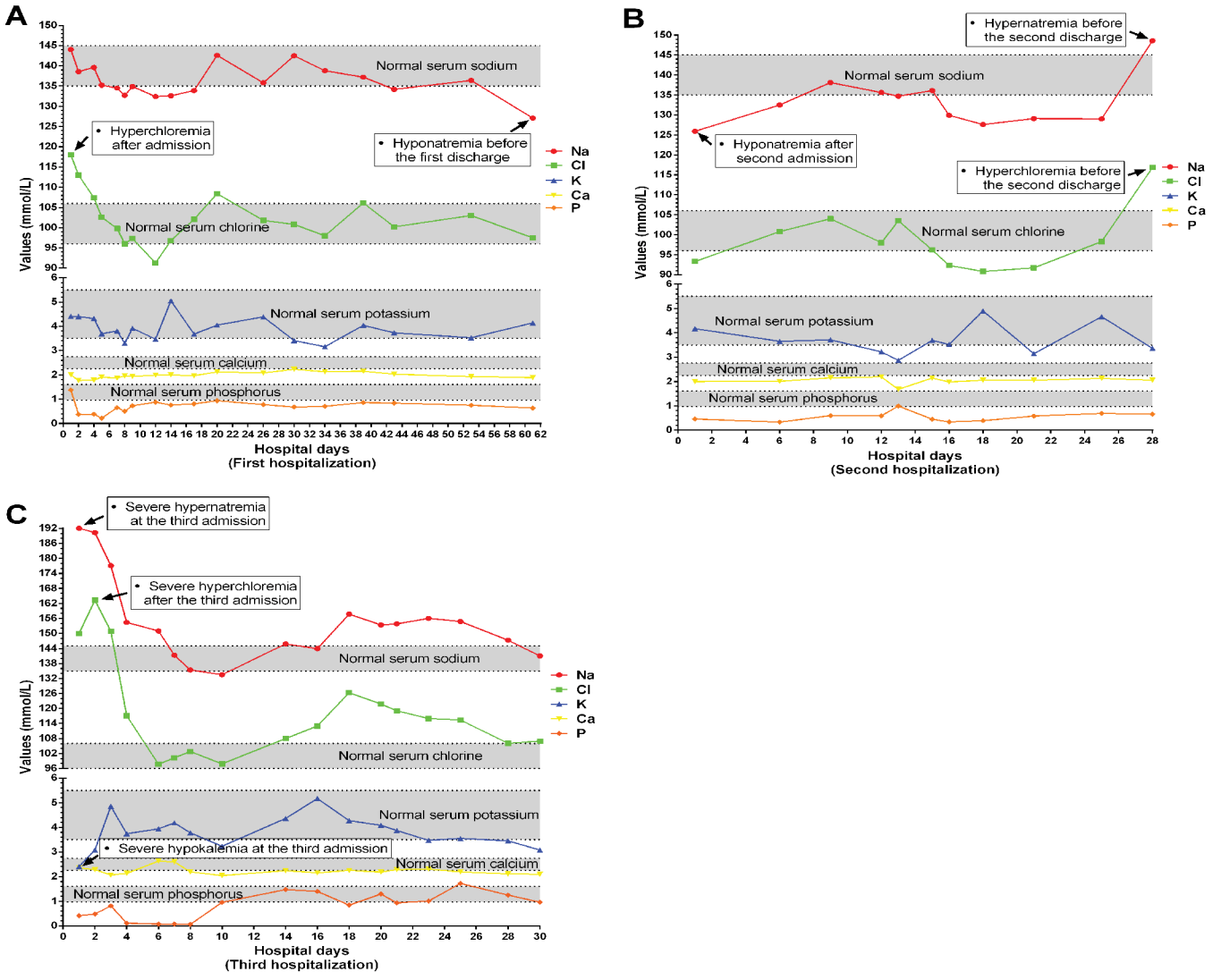

Figure 2. A series of serum electrolyte imbalances of this case in **(a).** first hospitalization, **(b).** second hospitalization and **(c).** third hospitalization.

Ca serum calcium; Cl serum chlorine, K serum potassium, P serum phosphorus; Na serum sodium

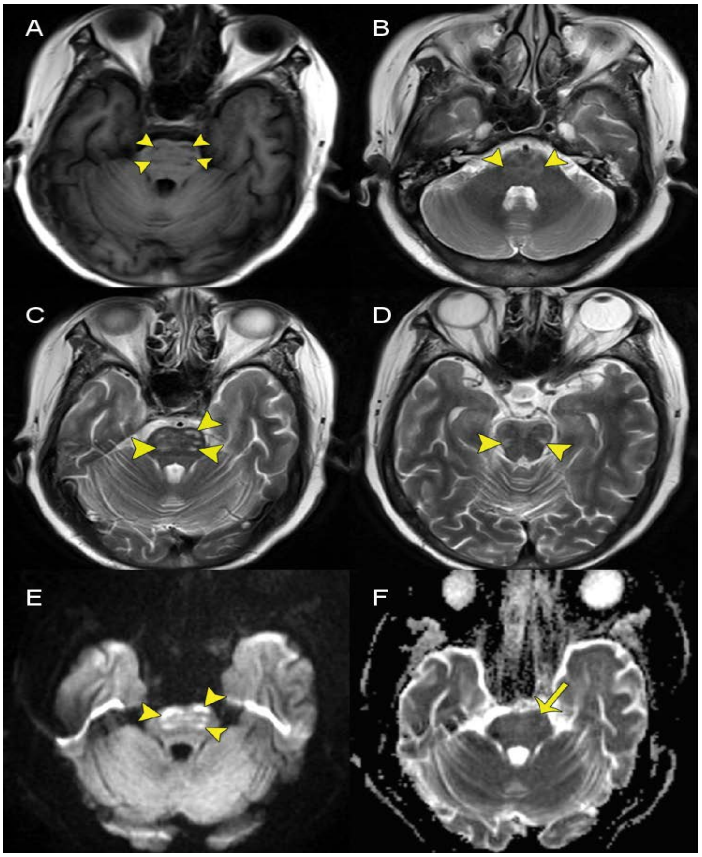

Figure 3. Brain MRI, performed 4.5 months after the acute pancreatitis event, **(a, arrowheads).** revealed relatively symmetric, spot-shape and patche-shape pontine lesions with hypointensity in T1-weighted and **(b, c, arrowheads)** hyperintensity in T2-weighted, as well as the **(d, arrowheads)** involvement of the midbrain. It exhibites facilitated restricted diffusion **(e, arrowheads)** at diffusion-weighted images. On apparent diffusion coefficient map, **(f, arrow)** these lesions are isointensity or mild hypointensity.

DISCUSSION

This 58-year-old woman presented a typical duration of severe and gallstone-associated acute necrotic pancreatitis for nearly five months. As for her three hospitalization, her course was complicated by transient hyperchloremia (first hospitalization), hypocalcaemia, hypophosphatemia, hyperglycaemia, profound and recurring hyponatremia and hypochloremia (second hospitalization), abdominal infection, pancreatic abscess removal operation and cholecystectomy (second hospitalization), marked diarrhea for two days before third hospitalization, severe and uncontrollable hypernatremia and hyperchloremia (third hospitalization), delayed onset renal insufficiency, persistent drowsiness, confusion, transient anisocoria and delayed onset speechless (mutism).

CPM is characterized by a demyelinating syndrome resulting in neurological impairment [1, 2, 3, 4]. Alcohol abuse or malnutrition with osmolarity disorder, leading to CPM, is a frequently presenting appearance [1, 2, 3, 4]. Myelinolysis following patients with AP is extremely rare, and the relationship between AP and CPM is obscure. To the best of our knowledge, only two cases have been reported as CPM after AP in prior literatures [3, 4]. The two cases have some features in common which consist of same gender (a 48-year-old male by R.J. Sherins *et al*. [3] and a 31-year-old man by Lou Grangeon *et al*. [4]) and a same medical history of chronic alcohol consumption. In fact, some symptoms on behavioral changes and the genesis of CPM in their patients may also be related to pathological effect of alcohol withdrawal [3, 4]. The different nature of our case is suggested by the lack of the medical background of chronic alcoholism and a female patient. Although the definite mechanism for the pathogenesis of CPM in our case is still elusive, it can be inferred that two reasons may be plausible explanations as the mechanism mediating the association between AP and delayed-onset CPM. First, progressive course of a severe acute necrotic pancreatitis and decreased food and water intake tend to cause severe electrolyte disturbance such as hypocalcemia, hypokalemia, hyponatremia and hypochloremia. In addition, severe abdominal infection and abscess formation in this case may further aggravate electrolyte imbalances. Upon her second hospitalization, prolonged and recurring hyponatremia and hypochloremia occurred, but in a slight hypernatremia combined with hyperchloremia before the second discharge [5]. Therefore, we cannot deny the possible associated pathological effect of precipitous and prolonged sodium correction with glucose saline [6, 7]. Second, diarrhea for two days (6-7 times per day) occurred just after second discharge, which was associated with dehydration and may be directly contribute to the deterioration of hypernatremia and hyperchloremia, shown as most critical levels of serum sodium of 192 mmol/L and serum chlorine of 150 mmol/L during the third admission. Hereafter, a hyperosmotic stress may

create a vasogenic edema and lead to a demyelination of the pontine glia, due to the worse pontine area's resistance to osmotic challenges [5, 6, 7]. Subsequently, brain MRI validated the final diagnosis for this case. Nevertheless, MR imaging features of our case are not exactly same as those findings in prior studies. Investigators in several CPM studies involving MR imaging have reported the classical findings of symmetric pontine "bat-wing" or large lamellar lesions [1, 2, 3, 4]. However, the lesions of this patient were visualized as multifocal spot-shape and patche-shape in both pontine and midbrain, other than obvious fusion areas.

According to the literature, AP is a possible cause responsible for CPM, and thereafter, psychiatric manifestations including altered mental status are sometimes possible [4, 8]. In our case, the neurological mental evolution is mainly associated with persistent drowsiness, transient anisocoria in both pupils and delayed onset mutism. Among them, transient anisocoria is relatively uncommon of CPM. The lesson is early recognition and consideration of the occurrence of CPM rather than other disorders such as acute stroke, when AP patients in the setting of severe electrolyte disturbance present with a spectrum of neurological and psychiatric symptoms. Given the low specificity of related clinical manifestations, MRI should be performed in time when this complication is suspected. Another important differential diagnosis related to AP patients is pancreatic encephalopathy [9], but this entity is usually normal or denotes non-specific lesions on MRI.

Clinically, CPM cases seem to have a poor outcome and the mortality rate of CPM is considered as approximately 25% [1, 2, 3, 4]. To date, there is still no specific treatment for this disease. In our case, we are convinced that the delayed onset of CPM is a main factor responsible for the death. Moreover, the prolonged duration of the patient's severe necrotic pancreatitis, associated with imbalances of internal environment, hyperglycemia conditions, severe infection and delayed onset renal insufficiency, also promote and aggravate the final outcome.

In conclusion, it is important to make the early diagnosis of CPM in AP patients (especially severe necrotic pancreatitis) if severe electrolyte disturbance and subsequently altered mental status or transient anisocoria occur, although delayed onset of CPM may be very rare following AP. Based on the high specificity imaging findings, MRI should be performed in time when this complication is suspected. In spite of the initial severity of AP, active conservative care and avoiding a precipitate limitation of management for delayed onset CPM are still warranted.

Patient Consent Statement: Patient's family members have provided informed consent for publication of the case.

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Conflicts of Interest

The authors report no conflict of interest.

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