Original Article

Clinical and pathologic characteristics of pancreatic necrosis in critically ill children

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BACKGROUND: Pancreatic damage in critically ill patients is associated with the progressive failure of multiple organs, but little is known about its clinical characteristics. At present, no guidelines are available for the diagnosis and management of pancreatic damage. This study was undertaken to analyze the clinical and pathologic characteristics of pancreatic necrosis in critically ill children, and to find some biological markers of pancreatic damage or pancreatic necrosis.

METHODS: We retrospectively reviewed the clinical data, laboratory results, and autopsy findings of 25 children, who were admitted to Hunan Children's Hospital, China from 2003 to 2009, and died of multiple organ failure. The autopsy revealed pancreatic necrosis in 5 children, in whom sectional or gross autopsy was performed.

RESULTS: The 5 children had acute onset and a fever. Two children had abdominal pain and 2 had abdominal bulging, flatulence and gastrointestinal bleeding. Four children had abnormal liver function, characterized by decreased albumin and 3 children had elevated level of C-reactive protein (CRP). B-ultrasonography revealed abnormal acoustic image of the pancreas in all children, and autopsy confirmed pancreatic necrosis, which may be associated with the damage of the adrenal gland, liver, lung, heart, spleen, kidney, intestine, thymus, mediastinal and mesenteric lymph nodes and other organs. Children 1 and 2 died of acute hemorrhagic necrotizing pancreatitis (AHNP); children 3-5 died of multiple organ dysfunction syndrome (MODS) due to pancreatic necrosis.

CONCLUSION: Pancreatic damage or pancreatic necrosis in critically ill children is characterized by acute onset, severity, short course, multiple organ damage or failure. It may be asymptomatic in early stage, and easy to be ignored.

KEY WORDS: Autopsy; Pancreatic damage; Pancreatic necrosis; Critically ill children

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INTRODUCTION

Critically ill children are often complicated with multiple organ damage due to primary diseases and potential diseases, leading to a high risk of death. Recent studies have been focused on myocardial damage, liver damage, kidney injury and kidney failure. The dysfunction of organs including the lung, kidney, brain, liver, and intestine as well as the hematopoietic and cardiovascular systems has been well studied, but still little attention has been paid to the pancreatic damage

of critical ill children. Biological signs of pancreatic damage are frequently observed in the patients even without pancreatic disease.^[1-4] Serum amylase and lipase levels are markers of pancreatic inflammation, and are used to diagnose acute pancreatitis. The critically ill patients are likely to have hyperamylasemia and hyperlipasemia. Elevated levels of amylase/lipase, pancreatic exocrine insufficiency, pancreatic injury, and other biological signs can be observed in 80% of the critically ill patients at the time of admission to intensive

care unit (ICU) with diagnosis of diseases other than pancreatitis.^[1] The elevation of serum amylase and/or lipase levels three or less than three times the normal values was not specific, and couldn't predict significant changes of the pancreas.^[5]

Pancreatic damage also occurs in some critically ill children. The results of autopsy showed that pancreatic injury varied from edema/inflammation to hemorrhage and necrosis. In this study we investigated the clinical manifestations and pathologic characteristics of pancreatic damage in children, and detected the relationship between pancreatic damage/necrosis and other organ damage.

METHODS

Patients

We retrospectively reviewed the clinical data, laboratory results and autopsy findings of 25 children who were admitted to Hunan Children's Hospital, China from 2003 to 2009 and died because of multiple organ failure. Autopsy demonstrated pancreatic necrosis in 5 children, who were enrolled in this study.

Among the 5 children, 2 were boys, and 3 girls; their age ranged from 9 months to 7 years, with a mean age of 3.81 years. Two children were directly admitted to PICU, 2 to the department of hematology, and 1 to the department of infectious diseases. Primary diseases included severe sepsis, disseminated tuberculosis, fulminant necrotizing hepatitis, systemic juvenile rheumatoid arthritis, and malignant histiocytosis.

Routine laboratory examinations after admission included tests of blood, electrolytes, liver and kidney function, myocardial enzymes, and C-reactive protein. The 5 children received symptomatic and supportive

treatments such as anti-inflammatory, antipyretic administration of fluid and electrolytes. They were also given anti-shock therapy or subjected to tracheal intubation and mechanical ventilation according to their clinical manifestations. They died from the deterioration of the illness.

Autopsy

Sectional or gross autopsy was performed in the 5 children. Tissues were taken from the brain, lung, heart, liver, spleen, and kidney. The tissues were fixed with 10% formalin, paraffin embedded, sectioned, and observed after HE staining. The autopsy study was approved by the Ethical Committee of the Hospital.

RESULTS

Clinical characteristics

The 5 children had a fever. Child 1 who had been already in shock at admission to PICU died an hour later although many rescue measures were taken. Child 2 had paroxysmal abdominal pain on the 6th day after admission. The pain was released after administration of drugs; a week later the pain reoccurred with vomiting till the next day. Subsequently shock appeared, and the child died 1 to 2 hours later. Children 3 and 4 had no pain at all, but abdominal bulging, abdominal distension, and gastrointestinal bleeding. They died rapidly. Child 5 had a disorder of electrolyte and internal environment characterized by low levels of kalium, sodium, chloride, metabolic alkalosis, etc.

Laboratory tests

Child 1 presented no laboratory data because she died within 2 hours after admission. The laboratory results of the other 4 children are shown in Table 1.

Table 1. Clinical and biochemical characteristics of pancreatic necrosis in the 5 critically ill children

Child	Clinical presentation	Severe progression	Laboratory tests												
			WBC ×10 ⁹ /L	HCT %	K ⁺ mmol/L	Ca ²⁺ mmol/L	BG mmol/L	TB μmol/L	ALB g/L	ALT IU/L	AST U/L	LDH IU/L	BUN mmol/L	Cr μmol/L	CRP mg/L
1	Vomiting, abdominal pain, dispirited	Shock, cardiopulmonary arrest	—	—	—	—	—	—	—	—	—	—	—	—	—
2	Fever, systemic bone joint pain	Shock, cardiopulmonary arrest	16.06	20.27	4.47	2.09	6.30	8.16	28.90	54.00	84.00	386.00	4.16	43.00	68.80
3	Fever, thrombocytopenia	DIC, heart failure	15.64	25.20	4.53	2.32	—	162.20	44.10	823.00	847.60	583.00	4.72	44.00	15.90
4	Cough, fever, diarrhea	Alimentary tract hemorrhage	1.09	19.66	4.73	1.80	21.20	70.03	23.00	59.00	335.00	2264.00	5.33	47.00	—
5	Recurrent cough, fever, tachypnea	Type II respiratory failure	5.25	23.43	2.78	1.57	1.36	15.85	11.30	28.00	149.00	1737.00	5.86	65.00	127.00

Normal reference ranges: WBC 4-10×10⁹/L, HCT 35%-45%, K⁺ 3.50-5.50 mmol/L, Ca²⁺ 2.10-2.70 mmol/L, BG (blood glucose) 3.8-6.2 mmol/L, TB (total bilirubin) 3.40-17.10 μmol/L, ALB (albumin) 35-55 g/L, ALT 0.00-40.00 IU/L, AST 0-40 U/L, LDH 0-450 IU/L, BUN 1.80-8.20 mmol/L, Cr 20-120 μmol/L, CRP 0-8.00 mg/L

Figure 1. Results of autopsy and pathological examination. A: considerable necrosis of the pancreas, with the remnants of normal glands at the lower left quarter (HE staining, original magnification $\times 100$); B: pancreatic necrosis, with the remnants of normal glands in the right side (HE staining, original magnification $\times 400$); C: focal necrosis of the pancreas, which is surrounded by the remnants of the normal gland (HE staining, original magnification $\times 400$); D: diffusive infiltration of lymphocytes around the necrotizing pancreatic acinar cells of the pancreas (HE staining, original magnification $\times 400$).

Peripheral white blood cell count was abnormal in 3 children, and a lower level of hematocrit was found in 4 children. The level of blood calcium was decreased in 3 children, and blood glucose abnormalities were seen in 2 children. In the 4 children there was abnormal hepatic function, whereas in the 3 children the level of albumin was significantly decreased, and C-reactive protein (CRP) was elevated.

Auxiliary examinations

B-ultrasonography showed hepatomegaly and cholecystitis in child 1, and splenomegaly, abdominal lymphadenopathy, seroperitoneum and liquid anechoic area in the right pelvic cavity in child 2. In child 3, flatulence appeared, and there were slightly reinforced echo in the parenchyma of the kidneys and the overfilling bladder. Child 4 demonstrated hepatosplenomegaly, tonic intensive echo in the parenchyma of the liver, edematous gallbladder wall, and mesenteric fluid. None of the 4 children had abnormal pancreas. Bone marrow stab and bone marrow biopsy revealed infected bone marrow and increased peripheral blood eosinophils in child 2; active proliferation of bone marrow, with decreased granulocyte hyperplasia, active erythroid proliferation and scattered platelet in child 3; bone marrow hypoproliferation in child 4 when granulocyte and erythroid proliferation was inhibited, but there were no megakaryocytes and platelets

because 92.0% were histiocytes.

Autopsy and pathological examination

Pancreatic necrosis was confirmed in all 5 children (Figure 1). Children 1 and 2 died of acute hemorrhagic necrotizing pancreatitis (AHNP); children 3-5 died of multiple organ dysfunction syndrome (MODS) due to pancreatic necrosis. In addition to pancreatic necrosis, the 5 children had the damage of multiple organs including the adrenal gland, liver, lungs, heart, spleen, kidneys, intestine, thymus, mediastinal and mesenteric lymph nodes (Table 2).

DISCUSSION

The incidence of pancreatic diseases has been increasing in recent years. Pancreatic damage would develop after the onset of primary diseases in some critically ill patients. The clinical manifestations of the damage include abdominal pain, vomiting, intestinal obstruction or other symptoms and signs. The levels of serum amylase and lipase are elevated separately or both in this condition, as seen in acute pancreatitis.^[6,7] Pancreatic damage may be transient; if primary diseases were cured, other clinical manifestations of pancreatic damage would have disappeared.^[8,9] However, other studies showed that pancreatic damage does not cause

Table 2. Pancreatic necrosis and damage of other organs in the 5 critically ill children

Child	Pathological diagnosis	Organ systems				
		pancreas	adrenal gland	liver	lungs	others
1	Sepsis, acute necrotizing pancreatitis, shock, cerebral edema, pneumorrhagia	Considerable necrosis of the pancreas. Obvious necrosis of glands around pancreatic islet, little normal tissues existed Lymphocytes infiltration	Obvious vacuolar degeneration of the gland cells, several hemorrhagic necrosis	Vacuolar degeneration of several liver cells, nuclear inclusion bodies existed	Pulmonary alveoli hemorrhage, lymphocytes infiltration into interstitial tissue	Myocardial mesenchymal and endomembrane: diffuse inflammatory cells infiltration Individual myocardial cells necrosis Lymph nodes: reactive hyperplasia; immunoblast hyperplasia in follicle and lymphatic sinus
2	Still's disease, acute necrotizing pancreatitis, shock, renal failure	Necrotic foci arranging in lamellar-shape appearance of the head, body, tail of pancreas. Little normal pancreatic acinar cells existed Lymphocytes infiltration, peripheral lymph nodes reactive hyperplasia	Lymphocytes infiltration into adrenal cortex and medulla	Obviously cellular edema, vacuolar degeneration, cholestasis Infiltration of lymphocytes and monocytes	Full of edema fluid in pulmonary alveoli, infiltration of lymphocytes and neutrophils into interstitial tissue	Myocardial mesenchymal: inflammatory cells infiltration Spleen: unclear structure, fibrin effusion, histiocytes and plasmacytes infiltration around blood vessels Kidney tubules: edema necrosis and abscission of epithelial cells Thyroid gland: edema and degeneration of alveoli, most of them ablated Lymph nodes: reactive hyperplasia and necrosis
3	Fulminant necrotizing hepatitis, pancreatic necrosis, congestion and necrosis of main organs (spleen, lungs, kidneys)	Obvious necrosis of the pancreas. No normal pancreatic acinar cells existed Lymphocytes infiltration	No evident abnormality	Absolute necrosis of the liver, no normal hepatic lobule or bile ducts Lymphocytes infiltration	Congestion and hemorrhage, lymphocytes infiltration into interstitial tissue	Myocardial mesenchymal: lymphocytes infiltration, several vacuolar degeneration Spleen: mussy structure, hemorrhage and necrosis Lymphocytes infiltration Kidney: hemorrhage and necrosis Mesenteric lymph nodes: reactive hyperplasia
4	Malignant histiocytosis	Focal necrosis of the pancreas Lymphocytes and allotypic histiocytes infiltration	Allotypic histiocytes infiltration	Fatty degeneration of liver cells, focal necrosis of the portal area, conglobate infiltration of lymphocytes and allotypic histiocytes	Edema fluid in pulmonary alveoli, hemorrhage, allotypic histiocytes infiltration into interstitial tissue	Myocardium: lymphocytes infiltration Spleen: unclear structure, focal necrosis Allotypic histiocytes infiltration into splenic sinusoid, renal cortex, thymus gland, lymph nodes, ileocolon
5	Disseminated tuberculosis	Cheesy necrosis of the pancreas.	Cheesy necrosis and tubercular nodules	Cellular edema and degeneration, hepatic lobule disappeared, cheesy necrosis and tubercular nodules	Cheesy necrosis and tubercular nodules	Myocardium: edema Spleen and lymph nodes: cheesy necrosis and tubercular nodules

serious clinical consequences in critically ill patients, but occurrence of pancreatitis would contribute to morbidity and mortality.^[1] Tribl et al^[2] found that the secretion of amylase, chymotrypsin, trypsin ($P<0.01$ each) and bicarbonate in duodenal fluid ($P<0.05$) was impaired in septic shock patients compared with healthy controls. The content of trypsin was different between sepsis patients and septic shock patients ($P<0.05$). Spearman's rank-order correlation coefficient analysis showed a significant difference between amylase secretion and APACHE III and SOFA scores ($P<0.01$). The SOFA score was also related to the secretion of trypsin ($P<0.05$). In our study, the 5 children rapidly developed severe hemorrhage and necrosis after acute pancreatic damage, and this made the treatment difficult.

Acute pancreatic damage can be secondary to bacterial and viral infections in many organs. The viruses or bacteria may enter the pancreas via blood or lymphatic tissues. Sheridan et al^[10] reported that

sepsis in burn patients could develop intraperitoneal infection such as acute cholecystitis, acute pancreatitis, and disappearance of enterokinesia. Hypotension and splanchnic hypoperfusion are the main causes of pancreatic damage. In 1978, Warshaw et al^[11] observed that the pancreas of patients with shock was significantly susceptible to ischemic injury. Animal studies also showed changes of microcirculatory blood flow in organs were heterogeneous, and pancreatic blood flow decreased more significantly than regional blood flow during early septic shock. Hildebrand et al^[12] used severe septic shock models of pigs to study dynamic distribution of microcirculatory blood flow in multiple splanchnic organs during septic shock, and they found that systemic and regional flows decreased by 50% during the first 240 minutes, while microcirculatory flow significantly decreased in the pancreas, liver, colon, kidney and stomach by 56%, 49%, 47%, 44%, and 41%, respectively. Endotoxin was found to play an important

role in septic shock patients with pancreatic damage, activating complements and coagulation systems, generating bradykinins and cytokines, and causing shock and damage to various organs including the pancreas.^[13] Pancreatic damage is associated with systemic metabolic diseases, such as diabetic ketoacidosis, systemic lupus erythematosus, Henoch-Schonlein purpura, hemolytic uremic syndrome and others.^[9, 14-16] L-asparaginase can cause pancreatic dysfunction in children with acute lymphoblastic leukemia (ALL). Pancreatic necrosis is one of the serious adverse effects, and the mortality of this type of pancreatitis is 2.5%. The effect of high doses of L-asparaginase on different tissues has been investigated, and other factors include exogenous CCK, fibroblast growth factor-7 and fibroblast growth factor-10 (FGF-7, FGF-10), keratinocyte growth factor receptor (KGFR).^[17,18]

In our study, children 1 and 2 were older than 3 years, and both complained of abdominal pain before death. Since it was difficult to define pancreatic damage, the levels of serum amylase, urine amylase and lipase were not determined. B-ultrasonography showed no signs of abnormal pancreas in the 5 children, suggesting difficulty in determining pancreatic damage. The 5 children died soon after the deterioration of their illness. Autopsy revealed pancreatic necrosis in all children, indicating pancreatic damage could aggravate primary diseases. Primary diseases of the 5 children included severe infectious diseases such as severe sepsis, disseminated tuberculosis, and fulminant necrotizing hepatitis, as well as underlying diseases like systemic juvenile rheumatoid arthritis, and malignant histiocytosis. The clinical symptoms varied, but all of the 5 children had a fever. Such fever in ICU is usually caused by infection or inflammation.^[3] The pathologic changes of the 5 children suggested that the following manifestations may be related to pancreatic damage: 1) acute onset, severity, or a short course of the disease before developing MODS; 2) inexplicable fever, vomiting, abdominal distension, ascites, mesenteric lymphadenopathy and abdominal fluid; 3) rapid pathologic changes, even development of shock; 4) rapid pathologic changes of respiratory failure, pulmonary edema, pulmonary hemorrhage; 5) hepatomegaly, abnormal liver function, decreased serum albumin, hemorrhage, thrombocytopenia or coagulation disorder; 6) lower level of calcium, higher level of blood glucose; and 7) higher level of CRP. CT is the "gold standard" for the diagnosis of pancreatic necrosis and peripancreatic collections, and also for the noninvasive diagnosis of pancreatic necrosis with an accuracy

rate of over 90 % when there is a rate of 30 % for glandular necrosis.^[19] Thus the diagnosis of pancreatic necrosis should be based on the clinical manifestations, biochemical parameters, and radiologic imaging.

In the 5 children we observed necrosis of liver cells, infiltration of lymphocytes, monocytes or allotypic histiocytes; reduced serum albumin, increased total bilirubin and transaminase; alveolar edema and hemorrhage, infiltration of lymphocytes, neutrophils in pulmonary interstitial tissue, respiratory disorders, and respiratory failure; spleen and renal necrosis; degenerated langendorff cells in thyroid gland, lymph nodes reactive hyperplasia. Adrenal necrosis and inflammatory cells infiltration were also seen in 4 of the 5 children. Further investigation is required to confirm their relationship.

Morphological changes of pancreatic damage are not obvious in critically ill children. None of the 5 children in our study showed abnormal pancreas although all but one were subjected to B-ultrasonography after admission. Since the pancreas is often ignored in the diagnosis of primary diseases in critically ill patients, laboratory examination of pancreas-related enzymes is rare. Hence studies have focused on the sensitivity and specificity of biological markers in the diagnosis of acute pancreatitis.^[20,21] Serum amylase and lipase are the most common indicators for acute pancreatitis. Blood biochemical examination is also of paramount importance. WBC>20×10⁹/L, 72 h CRP>150 mg/L, calcium<2 mmol/L, glucose>11.2 mmol/L (no history of diabetes), hematocrit (Hct)>44 may indicate pancreatic necrosis. Serum lactate dehydrogenase (LDH) is widely present in various tissues as a glycolytic enzyme, and it reflects cells damage. LDH is a sensitive marker of pancreatic necrosis.^[22] In our study, the LDH levels of 3 of the 5 children were elevated. In recent years, the diagnosis of pancreatitis and pancreatic injury has been improved because of the use of many new diagnostic techniques such as tests of procalcitonin (PCT),^[20] trypsinogen (TPG),^[21] trypsinogen activation peptide (TAP),^[23] pancreatic elastase-1 (E1),^[24] and leukocyte elastase (PMN-E).^[20] Of these methods, rapid urinary TPG-2 test and TAP test are considered as the most reliable and simple ways to early diagnose acute pancreatitis because they can predict accurately the severity of acute pancreatitis in 24 hours after appearance of symptoms.^[21,23] Studies have shown that severe ischemia, even if ischemia for a short time, can cause pancreatic damage and that the duration of ischemia is associated with the elevated pancreatic enzymes.^[25] Therefore, if pancreatic damage is highly suspicious, the levels of pancreatic enzymes and other sensitive indicators

should be dynamically monitored.

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