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Vlad Denis Constantin
Carol Davila University of Medicine and Pharmacy, constantindenis@yahoo.com

Alexandru Carâp
Carol Davila University of Pharmacy and Medicine

Bogdan Socea
Carol Davila University of Medicine and Pharmacy

Simona Bobic
St. Pantelimon Emergency Hospital

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Pancreatic encephalopathy- a rare complication of severe acute biliary pancreatitis

Vlad Denis Constantin[1], Alexandru Carâp[1], Bogdan Socea[1], Simona Bobic[2]
[1] Carol Davila University of Medicine and Pharmacy, Department of Surgery
[2] St. Pantelimon Emergency Hospital, Department of Surgery
Corresponding author: constantindenis@yahoo.com

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Abstract

Background. Pancreatic encephalopathy is a rare complication of severe acute pancreatitis, with high mortality, being difficult to diagnose and treat, thus requiring continuous research regarding its management.

Materials and Methods. Of 20 patients diagnosed with severe acute pancreatitis on admission at Department of Emergency and Admission (DEA), from January 1st 2010 to March 31st 2014, 5 cases complicated by pancreatic encephalopathy were analyzed using a descriptive observational, retrospective, single-centre study.

Results. The study shows different types of diagnostic algorithm and therapeutical approaches, in correlation with morbidity and mortality rates.

Conclusions. Our study highlighted the fact that speed is critical, early management being the key to outcome.

Introduction

Pancreatic encephalopathy, un uncommon complication of severe acute pancreatitis, was first described in 1941 by Rothermich and Von Haam and later by Vogel (1, 2). Neurological signs and symptoms may occur in the first two weeks of acute pancreatitis, irrespective of the etiology. It can have an acute onset, with convulsions, amaurosis, paresis, dysarthria, or it can have a progressive onset with beahvioural changes, psychomotor agitation, space and time dysorientation, visual or auditory hallucinations, affected consciousness that can lead to coma. These sympoms can have a cyclic evolution, with repeated relapses and remission.

As a complication of gallstone SAP, pancreatic encephalopathy (PE) is difficult to diagnose and treat, with a high mortality rate and poor prognosis. The onset of pancreatic encepalopathy in the early stage was regarded as a poor prognosis sign of severe acute pancreatitis (SAP), the pathogenesis still not being fully clarified. The development of PE in SAP may be a multi-factor process. Finding out the possible inducing factor represents an essential step for the management of PE in SAP.

For an accurate assessment of the severity of acute pancreatitis, several systems for classifying disease severity have been proposed, assisting in selection of patients (admission to a medical ward or to an intensive care unit) and also being applied at diagnosis in association with repeated clinical assessment, measurement of acute inflammatory markers, and computer tomography imaging. These include the Ranson criteria, Glasgow scales, Simplified Acute Physiology score and Acute Physiology And Chronic Health Evaluation II (APACHE II) score and the clinical BISAP score. The CT Severity Index (CTSI) derived by Balthazar grading of pancreatitis and the extent of pancreatic necrosis is largely used in describing CT findings of acute pancreatitis and serves as the radiological scoring system (3).

The etiology and pathogenesis have been continually investigated for centuries worldwide, being initiated by several factors, including gallstones, alcohol, trauma, infections and hereditary

factors. Acute biliary pancreatitis (ABP) is a potentially fatal disease caused by gallstones and represents approximately 35% to 70% of cases with pancreatitis worldwide (4). Several studies, however, reported a wider range, from 10% to 70% (5).

This article reviews these topics with a focus on surgical management, including appropriate timing and choice of interventions, the aim of the present study being to review the current management of gallstone pancreatitis, in cases developing PE, in "St. Pantelimon" Emergency Clinical Hospital, Bucharest, and to determine the extent to which the management is compliant with recently published consensus guidelines.

Materials and Methods

A descriptive observational, retrospective, single-centre study was carried out through the analysis of the medical records of consecutive patients admitted at the General Surgery Department of the "St. Pantelimon" Emergency Clinical Hospital, an academic hospital of the University of Medicine and Pharmacy "Carol Davila" in Bucharest, Romania, from January 1st 2010 to March 31st 2014 with a diagnosis of acute pancreatitis on admission at Department of Emergency and Admission (DEA).

Patients were treated, as well as written or oral informed consents for each procedure adopted were collected, according to the usual clinical practice.

Database and Study population

ICD-10 CM codes were used to identify cases of pancreatitis, biliary disease and encephalopathy. Inclusion criteria were: age ≥18 years; presence of recent neurological signs and/or dementia, diagnosis of severe acute biliary pancreatitis (any of the following three definitions: gallstones and/or sludge diagnosed on imaging (transabdominal or endoscopic ultrasound or computed tomography); in the absence of gallstones and/or sludge, a dilated common bile duct on

ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old); and alanine aminotransferase level >2 times higher than normal values, with serum alanine aminotransferase levels >aspartate aminotransferase level) and written informed consent (6, 7). Exclusion criteria were: patients with ongoing alcohol abuse or chronic pancreatitis, or pregnancy.

Data were recorded regarding demographics, diagnosis, predicted and actual severity of gallstone pancreatitis (index and recurrent attacks), the role of computed tomography and magnetic resonance scanning, the timing of cholecystectomy (open and laparoscopic), intraoperative cholangiography, duration of hospital stay, complications and mortality.

Statistics

The analysis of the data was made by means of descriptive statistical methods, using EpiInfo, a free software created by Centers for Disease Control and Prevention, Atlanta, USA and the Microsoft Office Excel software. Probabilities less than 0.05 were accepted as significant.

Results

In the aforementioned period 43 patients with final diagnosis of acute pancreatitis were identified, almost 60% (25 patients) presenting acute biliary pancreatitis, with 20 cases of severe disease, according to APACHE II and BISAP scoring systems, 5 of them being diagnosed with pancreatic encephalopathy.

At its most basic, severe acute pancreatitis is defined by organ failure lasting for more than 48 hours, according to modified Marshall scoring system, half of the study patients presenting clinically significant organ insufficiency, requiring urgent contrast enhanced CT for determination of the local extent of necrosis or local complications.

The degrees of severity (mild, moderately severe and severe) are also based on the presence or absence of local and systemic complications.

The local complications that occurred in the study population were: acute peripancreatic fluid collections in 2 cases, pancreatic pseudocysts in 3 cases, acute necrotic collections and walled-off necrosis in 5 cases, with 2 cases developing infected pancreatic necrosis, and biliary obstruction for 6 patients.

Renal, circulatory, or respiratory organ failure, or exacerbation of serious preexisting comorbidities related directly to acute pancreatitis are examples of systemic complications of acute pancreatitis with associated SIRS.

Pancreatic encephalopathy occured 4 hours to the 35th day after the onset of SAP: 1 patient within the first 24 hours, 1 case within 24 to 72 hours, 2 patients developed the complication in the 72 hours- 20 days interval and 1 case was diagnosed with PE after 20 days. The clinical symptoms were excitement (hallucination, fidget and handicaped directions), in 3 cases, and restrain (indifference, temporospatial dysorientation, coma), in 2 cases. Two patients showed modifications to some extent on electroencephalogram, the other 3 not being checked electroencephalographically. PE was the only complication in 1 case, and in the other 4 cases, local or systemic complications, such as pancreatic pseudocysts, acute necrotic collections or multiple organ failure were also present.

Three of the patients with PE had developed the neurologic dysfunction in the first 2 weeks after the onset of the SAP, with the remission of the symptomatology after treatment of the SAP.

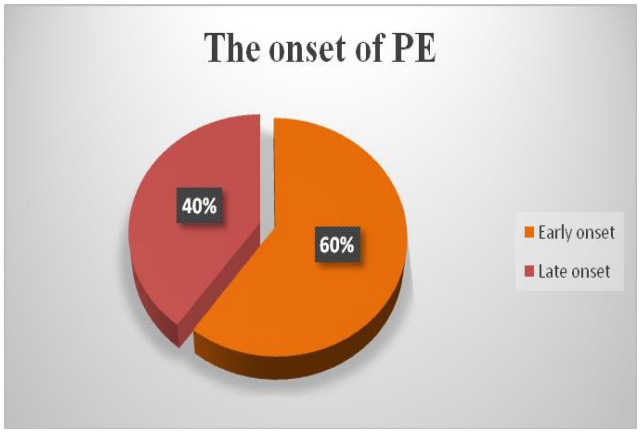

Figure 1. Time of the onset of the PE

In the present study 2 patients developed PE late in the evolution of the SAP, receiving intravenous vitamine B_1 treatment, alleviating the symptomatology (Figure 1).

The comorbid conditions existing in the study population were cardiovascular in 3 cases, respiratory in 3 cases, 2 patients

with renal comorbidity, 3 with hepatic comorbidity, 2 patients with diabetes and 1 with cancer, all 5 patients with PE presenting comorbidities (figure 2). Three patients suffered from multi-organ dysfunction syndrome and 2 patients developed abdominal compartment syndrome, with a sustained intra-abdominal pressure of more than 20 mm Hg.

The management for PE in ABP included life-support measures (including total parenteral nutrition [TPN], supply of vitamin B1, hemodialysis, mechanical ventilation [MV]), cholecystectomy, debridement of necrosis and minimally invasive (laparoscopic) approach to pancreatic necrosis.

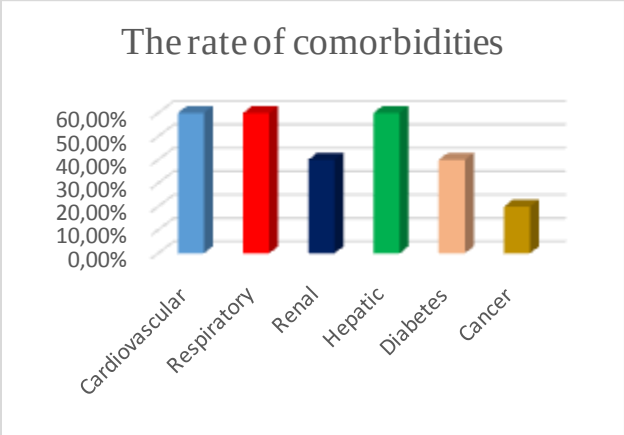

Figure 2. The frequency of comorbidities among the patient with PE.

The simple and important first steps in the management of severe biliary acute pancreatitis, thus preventing PE, are provision of adequate analgesia, efficient restoration of hypovolemia and correction of hypoxaemia.

All patients, except those with cardiovascular, renal or other comorbidities who required caution, had undergone early adequate volume resuscitation, using less than 4 L of lactated Ringer's solution (approximately 5-10 mL/kg per hour) in the first 24 hours, the optimum resuscitation being clinically evaluated by heart rate (<120bpm), mean arterial pressure (68-85 mmHg), urinary output (>1mL/kg per hour) and haematocrit (35-44%).

Antibiotics, such as quinolones, metronidazole and high-dose cephalosporins, were used in 2,out of the 5 patients with PE, with infected pancreatic necrosis, and 3, with extrapancreatic infection (urinary tract infection, pneumonia, catheter-acquired infection), who failed to improve after 7-10 days of hospitalization.

Total parenteral nutrition was considered in all 5 cases diagnosed with PE in SAP. In patients

with severe acute pancreatitis who deveoped PE, especially those with pancreatic necrosis, the cholecystectomy was delayed until a later time in the typically prolonged hospitalization in 4 cases, or after discharge, in 1 case.

Minimally invasive debridement after 4 weeks of hospitalization by laparoscopic approach was done in all 3 cases of walled-off necrosis, 2 of them requiring open surgery at a later time.

To characterize the impact of pancreatic encephalopathy in acute pancreatitis on the number of days of hospitalization, the analyses were made by stratifying the hospital stay into 2categories, by weeks of stay: 3 and greater than 3 weeks. The majority of the study population had a greater than 3 weeks hospitalization (4 patients-80%), 1 patients (20%) requiring 3 weeks hospitalization (figure 3). Within the 4 year study period, the mortality rate for the patients monitored has been calculated at 30% (6 cases of acute pancreatitis), with death occuring in 2 out of 5 patients with pancreatic encephalopathy (40%).

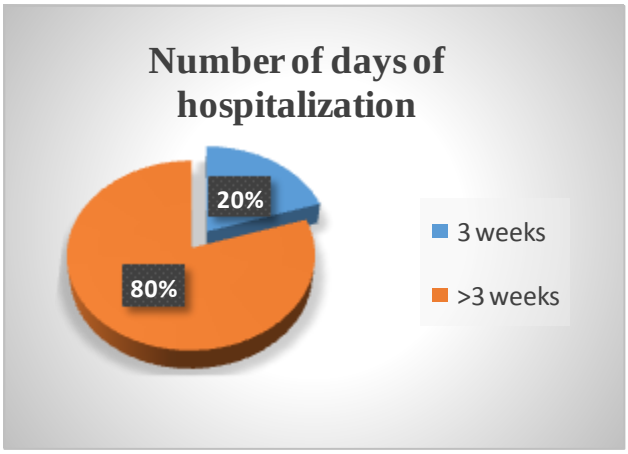

Figure 3. The distribution of study population according to the number of days hospitalization

Discussion

Pancreatic encephalopathy, as a syndrome of nervous and mental dysfunction secondary to metabolic abnormalities in severe acute pancreatitis, was first reported by Rothermich in 1941 (1).

According to medical literature (8), PE was classified into PE in early stage and late stage of SAP. In the early stage of SAP (the first 2 weeks), PE develops as a part of the multiple organ failure complication.

In the acute phase, pancreatic enzymes, such as trypsin, phospholipase A, chymotrypsin, lead to cerebrovascular changes (haemorrhage, nerve cell toxicosis, local encephalomalacia). A2 phospholipase is activated by trypsin and bile acids, converting pancreatic lecithin and cephalin into hemolytic lecithin and cephalin, with a strong toxicity, being capable of destroying membrane phospholipids of the blood-brain barrier, thus resulting in cerebral haemorrhage, encephalomalacia and demyelinization. Also, A2 phospholipase can hydrolyze the mithocondrial enzymes, blocking the oxygenation at a cellular level. (Goke B, Meyer T, Loth H. Caracterization of phospholipase A2 activity in aspirates of human pancreatic pseudocysts after isolation by reversed-phase high performance liquid cromatography (9).

Other important elements involved in the complicated evolution of SAP are cell factors, such as cytokines, tumor-necrosis factor α (TNF α), 1β- interleukin (IL-1β), IL-6 and IL-10 (10-14). Also, SAP complications, such as respiratory insufficiency and hypooxygenemia, can cause abnormal metabolism and cerebral edema.

The signs and symptoms are nonspecific and similar to those of other metabolic encephalopathies, making the diagnosis of pancreatic encephalopathy difficult. Among the 5 patients with PE included in the study, 3 had developed the neurologic dysfunction in the first 2 weeks after the onset of the SAP, all 3 having the symptomatology remitted after the treatment of the SAP.

In the late stages of SAP, PE occured after 2 weeks of evolution or during convalescence, one of the factors involved in the ethiopathonegesis being represented by inadequate vitamine B1seric levels or intake. In the present study 2 patients developed PE late in the evolution of the SAP and received intravenous vitamine B_1 treatment, allievating the symptomatology.

Acute biliary pancreatitis is the result of a transient obstruction of the bile and pancreatic ducts, causing reflux of bile and duodenal content and/or increase of hydrostatic pressure in the pancreatic

duct (15).The severity of the disease is determined by the extent and the intensity of the local and systemic inflammatory reaction. According to animal models and human studies, the duration of obstruction is a critical factor determining the severity, with pancreatic necrosis developing more often when the obstruction exceeds 48 hours (16, 17).

Due to the fact that Ranson score and modified Glasgow score have important limitations, containing data not routinely collected at the time of hospitalization and requiring 48 hours to complete, missing a potentially valuable early therapeutic window, the following scoring systems have been assigned to all the patients included in the study, in order to define severe pancreatitis: the APACHE II scoring system, the five-variables Bedside Index for Severity of Pancreatitis (BISAP) clinical scoring system, which predicts the in-hospital mortality (18), the presence of substantial pancreatic necrosis (>30% glandular necrosis on contrast enhanced CT), associated comorbidities and organ failure (Marshall scoring system).

Speed is critical, early management being the key to outcome. All patients, including the study cases with pancreatic encephalopathy, except those with cardiovascular, renal or other comorbidities, who required caution, had undergone early adequate volume resuscitation, the cornerstone of early management, thus reducing the rates of organ failure, morbidity and mortality, as demonstrated in Warndorf et al retrospective study of patients with acute pancreatitis (19).

The role of antibiotics in patients with severe ABP is to treat established infected necrosis, rather than prevent it, as demonstrated by Garg et al**.** (20), in accordance with the results of our study.

The present study has shown that patients provided oral feeding, early in the course of ABP, had a shorter hospital stay, decreased infectious complications, decreased morbidity and decreased mortality, this being, also, demonstrated by other authors (21). In patients with severe acute pancreatitis, especially those with pancreatic encephalopathy , the cholecystectomy and

minimally invasive debridement was delayed until a later time in the typically prolonged hospitalization or after discharge (22, 23).

Conclusions

Identification of patients at risk for developing PE early in the course of acute pancreatitis is an important step in improving the outcome. Early aggressive hydration should be provided to all patients, unless cardiovascular, renal or other related comorbid factors exist.

In severe AP, with PE, enteral nutrition is recommended. Parenteral nutrition should be avoided, unless the enteral route is not available, not tolerated, or not meeting caloric requirements.

For patients with severe ABP and PE, in order to prevent infection, cholecystectomy is to be deferred until neurological status improves, active inflammation subsides and fluid collections resolve or stabilize.

Although unstable patients with infected necrosis should undergo urgent debridement, current consensus is that the initial management of infected necrosis for patients who are clinically stable should be a course of antibiotics before intervention to allow the inflammatory reaction to become better organized.

The management for PE in ABP is represented by life-support measures, cholecystectomy, debridement of necrosis and minimally invasive (laparoscopic) approach to pancreatic necrosis.

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