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RAPID COMMUNICATION

Pancreatic encephalopathy and Wernicke encephalopathy in association with acute pancreatitis: A clinical study

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Abstract

AIM: To investigate clinical characteristics and therapy of pancreatic encephalopathy (PE) and Wernicke encephalopathy (WE).

METHODS: In a retrospective study of 596 patients with acute pancreatitis (AP), patients with PE were compared to those with WE in regards to history, clinical manifestation, diagnosis, treatment and outcome.

RESULTS: There were 93 patients with severe acute pancreatitis (SAP). Encephalopathies were discovered in 10 patients (1.7%). Six patients with PE all developed in SAP (6.5%), and three of them died (3% of SAP, 50% of PE). Four patients with WE developed in AP (0.7%), and two of them died (0.3% of AP, 50% of WE). Two patients with WE were treated with parenteral thiamine and survived. Global confusions were seen in all patients with encephalopathy. Ocular abnormalities were found. Conjugate gaze palsies were seen in 1 of 6 (16.7%) patients with PE. Of 4 patients with WE, one (25%) had conjugate gaze palsies, two (50%) had horizontal nystagmus, three (75%) had diplopia, and one (25%) had myosis. Ataxia was not seen in all patients. None of patients with WE presented with the classic clinical triad. CSF examinations for 2 patients with WE showed lightly-increased proteins and glucose. CT and MRI of the brain had no evidence of characteristic abnormalities.

CONCLUSION: PE occurs in early or reiteration stage of SAP, and WE in restoration stage of SAP/AP. Ocular abnormalities are the hallmarks of WE, and horizontal nystagmus is common. It is difficult to diagnose earlier an encephalopathy as PE or WE, as well as differentiate one from the other. Long fasting, hyperemesis and total parenteral nutrition (TPN) without thiamine are main causes of thiamine deficiency in the course of pancreatitis.

Key words: Pancreatic encephalopathy; Wernicke encephalopathy; Acute pancreatitis; Thiamine; Total parenteral nutrition

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INTRODUCTION

Pancreatic encephalopathy (PE) is an uncommon complication of acute pancreatitis (AP). PE, which is one of multiple organ dysfunction syndrome (MODS), generally occurs in early stage of severe acute pancreatitis (SAP) and has a high mortality of 57%[1]. But in the last or restoration stage of AP, neurological complications are mostly Wernicke encephalopathy (WE) which results from long fasting, hyperemesis and total parenteral nutrition (TPN) without thiamine (vitamin B1, Vit B1). A large dose of Vit B1 is certainly effective for WE. However, it is difficult to diagnose earlier an encephalopathy as PE or WE, as well as differentiate one from the other. Recent studies[2] have shown that WE is poorly recognized by clinicians, even when features of the classic triad of symptoms are evident. Recognition of the progressive nature of the disease is critical because the mortality rate is as high as 10% to 20%[3-5], and treatment may correct all abnormalities. This study demonstrates many of the common clinical characteristics of WE and the diagnostic dilemma physicians encounter when confronted with WE. By reviewing our clinical experience, we can learn many lessons which are beneficial for physicians, not just those who care for patients with PE.

MATERIALS AND METHODS

Patients and methods

A retrospective study was conducted on 596 patients with AP hospitalized at China PLA General Hospital over a 10-year period from Jun 1993 to Dec 2003. There were 93 patients with SAP. A chart was reviewed containing the following demographic and clinical data: age, sex, clinical

Table 1 Manifestation and outcome of patients with encephalopathy

No.	Sex	Age (yr)	Primary disease	Manifestation of encephalopathy	Diagnosis	Treatment/Outcome
1	M	29	SAP with ARDS.	4th d of onset, restlessness, haziness, delirium. Pathological sign negative.	PE	Diazepam, haloperidol. Recovery
2	F	51	SAP	At onset, haziness, delirium.	PE	Recovery
3	M	41	SAP with ALI.	4th d of onset, restlessness, sleepiness, haziness.	PE	Recovery
4	M	34	SAP with pseudocyst bleeding	SAP for 3 mo, 3rd d after pseudocyst operation, hallucination, delirium, conjugate gaze palsies, coma, suspected Kernig sign. Diffused pancreatic necroses.	PE	Death
5	F	42	SAP with ALI and shock	9th d of onset, delirium, unconsciousness.	PE	Death
6	M	31	SAP with ARF and ARDS.	33rd d after onset, restlessness, hebetude, unconsciousness, delirium.	PE	Death
7	F	37	Recovery Phase of AP	Protracted vomiting. No supplement of $VitB_1$. 36th d after onset, diplopia, tinnitus, apathy, dizziness, horizontal nystagmus. CSF negative, MRI negative.	WE	$VitB_1$, B_{12} im. Recovery after 4 d
8	M	48	Recovery Phase of SAP, with ALI and pseudocyst	45th d of onset, diplopia, sleepiness, haziness, horizontal nystagmus, spatial disorientation, decreased tendon reflex.	WE. Once suspected PE	Fasting for 51 d, no $VitB_1$ in TPN for 44 d. Recovery after 4-day's administration of $VitB_1$
9	M	37	Acute recurrent pancreatitis with pseudocyst	Long fasting, no supplement of $VitB_1$. Nausea, vomiting, dizziness, hypomnesia, alalia, diplopia, amentia, coma. Conjugate gaze palsies, active tendon reflex, ankle clonus positive. CSF: total cells 134, WBC 2; glucose, protein increased lightly. MRI: suspected focus of brain stem.	WE. Once suspected PE and encephalitis	Dexamethasone ineffective. Administration of $VitB_1$, 400 mg/d. Death
10	F	40	Recovery phase of AP	42nd d after onset, vomiting, dizziness, alalia, trance, amentia, sleeplessness, hyperspasmia, coma. Myosis, decreased tendon reflex. Pathological signs negative. CSF: protein positive; total cells 180, WBC 0; glucose, protein increased lightly.	WE. Once suspected viral encephalitis	Dexamethasone, acyclovir ineffective. Respirator. Death

ALI: acute lung injury; ARF: acute renal failure; ARDS: acute respiratory distress syndrome; CSF: cerebrospinal fluid; TPN: total parenteral nutrition.

signs, history, imaging, treatment, hospital course and outcome. Patients with PE were then compared to those with WE in regards to history, clinical manifestation, diagnosis, treatment, and outcome.

RESULTS

Encephalopathy was discovered in 10 patients (1.7%), including 6 males and 4 females with a mean age of 39.0 years (from 29 to 51 years old). Six patients with PE all developed from SAP (6.5%); three patients died (3% of SAP, 50% of PE). Four patients with WE developed from AP (0.7%); two patients died (0.3% of AP, 50% of WE). Two patients with WE were treated with parenteral Vit B1 and survived. PE occurred in early or reiteration stage of SAP, and WE in restoration stage of SAP/AP.

The clinical features were also reviewed in all patients (Table 1). Global confusions were seen in all patients with encephalopathy. Ocular abnormalities were also found. Conjugate gaze palsies were seen in 1 of 6 (16.7%) patients with PE. Of 4 patients with WE, 1 (25%) was seen conjugate gaze palsies, 2 (50%) horizontal nystagmus, 3 (75%) diplopia, and 1 (25%) myosis. Ataxia was not seen in any of the patients. None of the patients with WE presented with the classic clinical triad. CSF examination was performed on 1 patient with PE and showed negative, whereas it was done on 2 patients with WE and showed lightly-increased proteins and glucose. Of the 10 patients, 5 had CT scan of the brain and none had evidence of characteristic abnormalities. MRI was performed on 2 patients with WE and only 1 had some suspected changes of brain stem. Long fasting, protracted vomiting and TPN without Vit B1 supplement were main causes of Vit B1 deficiency, which crucially resulted in WE.

DISCUSSION

PE, first described by Lowell in 1923, refers to the abnormalities of mental status in patients with AP. Abnormalities of mental status, such as spatial disorientation, trance, agitation with delusion and hallucination, were defined as PE by Rothermich[6,7]. In China, PE had a high mortality of 57%[1], and main causes of death were shock, MODS, renal failure and ketoacidosis. At present pathogenesis of PE is unclear yet, and most scholars think that it is related to phospholipase A (PLA) activation, hypovolemia, multiple organ failure, electrolyte disturbance and cytokine effect in the course of AP[8]. In recent years, it has been gradually known that PLA in pancreatitis is not only the primary factor causing pancreatic necrosis, but also crucial substance resulting in PE[9]. Johnson *et al*[10] reported a male patient with AP. Cerebral fat embolism was established as the cause of his death. They thought that PE might be due to hypoxia secondary to pulmonary fat embolism, cerebral fat embolism, or the complicating syndromes of disseminated intravascular coagulation or hyperosmolality.

PLA2 damages structural phospholipid of brain cell membrane; platelet activating factor (PAF) increases intracerebral vascular permeability with brain edema and demyelinization of grey and white matter. PE is primarily due to the demyelinization of the cerebral grey and white matter caused by PLA2, which can induce increased vascular permeability. The intravascular osmotic pressure decreases and the brain becomes more vulnerable to transudation, and finally brain edema is resulted[11].

With proper treatment, the recovery in patients aged

below 40 is uneventful. Those older than 60 especially those with a previous history of cerebral infarction may have some sequela[11]. Ruggieri *et al*[12] presented a patient of 43-year-old man who, after an acute episode of pancreatitis, experienced five relapses, with alternating focal signs. The patient had improved, but cognitive impairment persisted after a 7-year follow-up.

A report[13] of Boon *et al* showed the usefulness of MRI in the diagnosis of this disorder. Patchy white matter signal abnormalities, resembling plaques seen in multiple sclerosis, might reflect the lesions that were found in the cerebral white matter of post-mortem confirmed patients.

Estrada *et al*[7] conducted a prospective study on 17 patients with AP. PE was discovered in 6 patients (35%). A direct relationship was found to exist between the PE condition and an increase in CSF-lipase, and electroencephalographic changes were nonspecific. The encephalopathy did not affect the course of AP, and showed no relationship to type of treatments involved. Whereas the severity of AP was not related to the presence or absence of encephalopathy.

Our study revealed that PE occurred in early or reiteration stage of SAP and had a global confusional state for 2-7 d. Some patients had ocular abnormalities. There was no specific therapy for PE. Treatment of AP was the key to prevention and therapy of PE.

The clinical trial of Qian *et al*[14] revealed that recombinant human growth hormone (rhGH) had a therapeutic effect for patients with early PE; rhGH combined with somatostatin might reduce occurrence of PE. However, the mechanism is unclear yet.

WE is an uncommon neurological disorder characterized by a triad of ocular abnormalities, ataxia, and global confusional state. In 1881, Carl Wernicke initially described punctate hemorrhages affecting grey matter around the third and fourth ventricle and aqueduct of Sylvius and designated it "polioencephalitis hemorrhagica superioris"[15]. Experimental and clinical studies have demonstrated that WE results from a deficiency of thiamine (vit B1), an essential coenzyme in intermediate carbohydrate metabolism[16,17].

The mortality rate ranges from 10% to 20%. At autopsy, patients may have pin-point hemorrhages in the mamillary bodies, hypothalamus, and paraventricular regions of the thalamus, around the aqueduct and beneath the floor of the fourth ventricle[3-5]. A retrospective study of Ogershok *et al* showed similar pathological lesions at autopsy[2].

Although WE is thought to be a disease that occurs primarily in the alcoholic population, Lindboe's autopsy study revealed 12 (23%) of 52 patients in nonalcoholic population[4]. Some of the nonalcoholic conditions associated with this disorder include prolonged intravenous feeding, hyperemesis gravidarum, anorexia nervosa, refeeding after starvation, thyrotoxicosis, regional enteritis, malabsorption syndromes, hemodialysis, peritoneal dialysis, uremia, HIV, malignancy, and gastroplasty with postoperative vomiting[15,18,19].

WE is a life-threatening condition that is avoidable by early recognition and administration of thiamine. Recognition of this disorder remains difficult because very few patients actually present with the classic signs of nystagmus, ataxia, and global confusion. To deal with this diagnostic problem for chronic alcoholics, new operational criteria were published in 1997. The diagnosis criteria require 2 of the following 4 signs: dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, and either an altered mental state or mild memory impairment[20]. Harper *et al*[3] indicated that only about 16% had this classic triad, and 19% had no clinical signs. On Harper's review of both clinical and pathology studies, a wide range of the presentation with these signs was revealed. Ocular signs were present in 29% to 93%, ataxia in 23% to 70%, and mental changes in 82% to 90%.

In fact, none of the CT studies helps clinicians with the diagnosis. MRI can reveal areas of signal change in the paraventricular regions of the thalamus and in the paraventricular regions of the midbrain with this disorder. Dilation of the third ventricle and atrophy of the mamillary bodies can also be seen. MRI is helpful in confirming the diagnosis of WE; however, the absence of abnormalities does not exclude the diagnosis. The sensitivity of MRI is 53%, whereas the specificity is 93%[21-24].

WE is a medical emergency and treatment consists of hospital admission and administration of intravenous thiamine. The clinical response after administering thiamine is usually striking and rapid enough to be virtually diagnostic[3]. As few as 2 mg of thiamine may be enough to reverse the ocular symptoms (which generally begin to improve in 1-6 h), however, initial doses of at least 100 mg are usually administered. Ataxia and acute confusional state may resolve dramatically, although improvement may not be noted for days or months. We suggest starting thiamine prior to treatment with IV glucose solutions, and continuing until the patient resumes a normal diet. Magnesium is an indispensable cofactor in thiamine-dependent metabolism. In hypomagnesemic states, normal function of thiamine pyrophosphate, the active coenzyme containing thiamine, does not occur. Consequently, the final step in treating WE is correcting magnesium deficiency. The prognosis of WE depends on the stage of disease and prompt institution of thiamine[15,16].

Our study revealed that WE continued to be a rare but life-threatening condition often overlooked in the course of AP. WE occurred in restoration stage of SAP/AP. Ocular abnormalities were the hallmarks of WE, and horizontal nystagmus was common. Long fasting, hyperemesis and TPN without Vit B1 in the course of AP were main causes of Vit B1 deficiency. Two patients with WE were treated with parenteral Vit B1 and survived; two patients once misdiagnosed as PE or cephalitis.

Chen *et al*[1] analyzed 185 patients with AP complicated with encephalopathy. They thought that encephalopathy appearing in the early course of AP was PE. PE had a high mortality of 57%. WE appeared in the late course of AP (> 2 wk or in recovery period), and had a mortality of 33% (26/78). The difference between the two groups was significant ($P < 0.01$). Supplement of thiamine in time resulted in lower mortality in WE. Therefore, they suggested that patients who have been on fasting for a long time (more than 10 d) should be given thiamine intramuscularly in case WE occurs.

Winslet *et al*[25] reported a young obese female with AP complicated by pseudocyst formation and intermittent

gastric outlet obstruction, who had been maintained on high-calorie enteral feeds, developed a sudden onset of confusion and ophthalmoplegia associated with papilloedema and retinal haemorrhages. A possible diagnosis of WE was made. The patient was treated with parenteral thiamine, and survived. The authors suggested that any patient with suspicious or unusual neurological symptoms and signs associated with possible malnutrition, hyperemesis or malabsorption should be given intravenous thiamine without delay to avoid the potential morbidity and mortality associated with undiagnosed WE.

In summary, it is difficult to diagnose earlier PE and WE complicating AP. In case differential diagnosis of PE and WE is baffled, Vit B1 diagnostic treatment may be useful: patients' condition of WE is supposed to improve after injected Vit B1 (100 mg/d) therapy for 1-3 d. If a patient, in the course of pancreatitis, has suspicious or unusual neurological symptoms and signs, a possible diagnosis of encephalopathy should be made, and the patient should be given intravenous thiamine without delay to avoid the potential morbidity and mortality associated with undiagnosed WE.

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