Risk factors for acute pancreatitis in patients with severe motor and intellectual disabilities

*Akiko Tamasaki, Yoko Nishimura, Noriko Kondo, Kentaro Shirai, Yoshihiro Maegaki, Kousaku Ohno

Division of Child Neurology, Institute of Neurological Science, Faculty of Medicine, Tottori University, Yonago, Japan

*Corresponding author:

Akiko TAMASAKI, Division of Child Neurology, Institute of Neurological Science, Faculty of Medicine, Tottori University

36-1 Nishi-cho, Yonago, 683-8504, Japan

Tel: +81 859 38 6777

Fax: +81 859 38 6779

E-mail address: holbergs@nifty.com

Abstract

Aim: Acute pancreatitis in patients with severe motor and intellectual disabilities (SMID) is a rare but life-threatening condition. Possible causes of acute pancreatitis in these patients including valproic acid therapy, hypothermia and nasoduodenal tube feeding, have not yet been investigated in detail. This study aimed to investigate the risk factors for acute pancreatitis in patients with SMID. Methods: We reviewed 5 SMID patients with acute pancreatitis and 15 SMID patients without acute pancreatitis. Age; serum levels of total cholesterol, triglyceride, total protein, and albumin; height; body weight; body surface area; body mass index; daily calorie intake; daily calorie intake per unit of body mass surface area; daily calorie intake per kilogram body weight; and valproic acid usage were examined. Results: Statistically significant difference was observed in serum albumin levels between (P = 0.026) the two groups. Conclusion: The mechanism of acute pancreatitis in these patients was considered as pancreatic morphological change, acinar damage, and elevated serum trypsinogen levels caused by malnutirition. It is likely that acute pancreatitis in patients with SMID occur by the similar mechanism with anorexia nervosa and malnourished patients. To prevent acute pancreatitis in these patients, it is important to maintain adequate nutritional status.

Key Words: severe motor and intellectual disabilities, acute pancreatitis, malnutrition, hypoalbuminemia

1. Introduction

Acute pancreatitis in patients with severe motor and intellectual disabilities (SMID) may be life-threatening. Moreover, it can be difficult to diagnose because signs and symptoms are usually nonspecific: fever, abdominal distention, gastric bleeding, bilious vomiting, and diarrhea. A delay in diagnosis and treatment can have very serious, even fatal. Various risk factors for acute pancreatitis occurring in patients with SMID have been reported: valproic acid (VPA) therapy,[1] scoliosis, nasoduodenal tube feeding, and hypothermia.[2] However the mechanisms by which these factors work have not been examined in details. This study examined the risk factors of acute pancreatitis in patients with SMID to aid in the prevention of this critical condition.

2. Patients and methods

SMID patients with acute pancreatitis (n = 5: 2 males, 3 females) and without acute pancreatitis (n = 15: 8 males, 7 females) were identified retrospectively from a database containing information about all children who visited our division from 2007 to 2012. All patients were bed-ridden and diagnosed with SMID patinets. Table 1 displays the clinical profiles of patients with SMID in acute pancreatitis group (pancreatitis group). Underlying diseases in SMID patients without pancreatitis (control group) included hypoxic-ischemic encephalopathy (n = 2), severe neonatal

asphyxia (n = 4), microcephaly and brain anomaly (n = 2), bacterial meningoencephalitis (n = 1), sepsis associated encephalopathy (n = 1), cerebral palsy (n = 1), Sotos syndrome (n = 1), congenital central hypoventilation syndrome (n = 1), Niemann-Pick disease type C (n = 1), and adrenoleukodystrophy (n = 1). In the pancreatitis group, acute pancreatitis recurred four times in one patient and eight times in another patient; in these two patients abdominal echo and magnetic resonance cholangiopancreatography were performed. No anomalous arrangement of pancreaticobiliary ducts or biliary duct dilatation were recognized. Antibody levels to cytomegalovirus, varicella-zoster virus, coxsackie virus, Epstein-Barr virus, and hepatitis A, B, and C virus, were examined in one of these patients, but no elevated levels were detected.

In two patients with SMID in pancreatitis group, the serum VPA levels at the onset of acute pancreatitis was 116.4 μ g/ml and 63.1 μ g/ml, the duration of VPA treatment was 7 years and 10 months, 2 years and 6 months, respectively. In two SMID patients medicated by VPA in control group, the serum concentration of VPA was 75.6 μ g/ml and 23.5 μ g/ml, the duration of VPA treatment was 3 years and 6 months, 4 years and 3months, respectively.

Diagnosis of acute pancreatitis was made on the basis of laboratory findings (elevation of serum pancreatic amylase and lipase) and abdominal computed

tomography (CT) findings (pancreatic enlargement and infiltration of surrounding fat). No gallstone revealed on abdominal CT in any patient.

Patients were compared in terms of following parameters: age; sex; respiratory care; feeding methods; valproic acid therapy; serum levels of total cholesterol, triglyceride, total protein and albumin; height; body weight; body surface area (BSA); body mass index [BMI, calculated by using the following equation: weight (kg)/height $(m)^2$]; daily calorie intake; daily calorie intake per unit of BSA; daily calorie intake per kilogram of body weight. In the pancreatitis group, the serum levels of total cholesterol, triglyceride were selected at the onset of acute pancreatitis and the serum levels of total protein, albumin were selected that had been collected when patients were in good general condition one or two months before the onset of acute pancreatitis. For the two patients with recurrent disease in the pancreatitis group, quantitative data were selected that had been collected before the first episode of acute pancreatitis.

Statistical analysis

Quantitative data were retrospectively examined using the Mann-Whitney U test. The chi-square test was applied for comparison of results by sex, respiratory care, feeding methods, VPA therapy. Quantitative and qualitative data except for VPA therapy was analyzed after excluding the SMID patients medicated by VPA. The

significance level was determined as $P < 0.05$.

3. Results

Significant difference in serum albumin level was observed ($P < 0.05$) between patients in the pancreatitis and control groups. No significant difference in age, sex, respiratory care, feeding method, VPA therapy, height, body weight, BSA, BMI, daily calorie intake, daily calorie intake per unit of BSA, daily calorie intake per kilogram of body weight, serum total protein, total cholesterol and triglyceride level were evident between groups (Tables 2 and 3).

4. Discussion

Acute pancreatitis is triggered by pancreatic autodigestion, which is followed by activation of pancreatic enzymes. Some etiologies of acute pancreatitis were known, including viral infection, multisystem disease, hyperlipidemia, drugs, trauma, autoimmune disease, congenital anomalies of the pancreaticobiliary system, malnutrition.[3] VPA is known as one of the drug caused with acute pancreatitis. In this study, the risk of VPA therapy was untried because the numbers medicated by VPA were poor. The past articles show that dose, duration of treatment, serum VPA levels are no concern of acute pancreatitis.[1, 4] Additionally there is no evidence that VPA is

an independent risk factor of acute pancreatitis.[5]

Recurrent acute pancreatitis in anorexia and bulimia[6] and acute and chronic pancreatitis in patients with protein energy malnutrition were previously reported.[7] Cleghorn et al. reported that acinar cell damage and ductal obstruction were reflected by higher levels of serum trypsinogen in moderately and severely malnourished patients than in normally nourished patients.[8] Moreover, marked acinar cell atrophy has been demonstrated in malnourished animals,[9] and increased zymogen granule release has been found in malnourished patients.[10] A protein-deficient diet causes a decrease in size and number of zymogen granules in acinar cells because zymogen granules are produced from protein; this results in acinar cell destruction.[11, 12] In addition, protein energy malnutrition (marasmus, kwashiorkor) may lead to oxidative damage to the pancreas in a system with poor antioxidant reserves and inflammatory damage to the pancreas by elevation of the cytokines interleukin-1, interleukin-6, and tumor necrosis factor- α .[7]

In this study, serum albumin levels in SMID patients with acute pancreatitis were significantly lower than those in SMID patients without acute pancreatitis. No protein extravasation or urinary protein excretion were evident, probably because these laboratory data were collected at a time when the patients were in good general condition. The results of urine protein tests in the patients included in this study were

negative (data not shown). Thus, in this study data for serum albumin levels were considered as a reflection of patients' nutritional status. However, a more detailed evaluation of nutritional status is required, including examination of rapid turnover protein; prealbumin, transferrin, and retinol binding protein for conclusive information on nutritional status in patients with SMID.

Protein breakdown in malnourished patients reduces the body's supply of amino acids and results in decreased synthesis of plasma proteins.[13] Moreover, in patients on long-term bed rest, muscle wasting is caused by protein breakdown as well. In addition, recurrent infection increases the body's protein consumption. This inadequate protein turnover may result in hypoalbuminemia in patients with SMID who are malnourished, bed-ridden, and subject to recurrent infection.

Causes of acute pancreatitis in patients with SMID may be related to pathological changes in the pancreas occurring as a result of malnutrition similar to those observed in patients with anorexia nervosa and protein energy malnutrition. Fortunately, pancreatic malfunction due to malnutrition is reversible.[11] Adequate nutritional control and minimizing the opportunity of infections may improve pancreatic function and prevent development of acute pancreatitis.

In conclusion, the results of this study indicate that hypoalbuminemia are risk factors for acute pancreatitis in patients with SMID. Adequate management of nutritional

status in patients with SMID is important to prevent development of pancreatitis.

Potential Conflict of Interest Report

The authors have no financial or personal relations that could pose a conflict of interest.

References

1 Grauso-Eby NL, Goldfarb O, Feldman-Winter LB, McAbee GN. Acute pancreatitis in children from valproic acid: case series and review. Pediatr Neurol 2003;28:145-8.

2 Hauer JM. Central hypothermia as a cause of acute pancreatitis in children with neurodevelopmental impairment. Dev Med Child Neurol 2008;50:68-70.

3 Nydegger A, Couper RT, Oliver MR. Childhood pancreatitis. J Gastroenterol Hepatol 2006;21:499-509.

4 Sinclair DB, Berg M, Breault R. Valproic acid-induced pancreatitis in childhood epilepsy: case series and review. J Child Neurol 2004;19:498-502

5 Norgaard M, Jacobsen J, Ratanajamit C, et al. Valproic acid and risk of acute pancreatitis: a population-based case-control study. Am J Ther 2006;13:113-7

6 Morris LG, Stephenson KE, Herring S, Marti JL. Reccurent acute pancreatitis in anorexia and bulimia. JOP 2004;5:231-4.

7 Wesson RN, Sparaco A, Smith MD. Chronic Pancreatitis in a patient with malnutrition due to anorexia nervosa. JOP 2008;9:327-31

8 Cleghorn GJ, Erlich J, Bowling FG, et al. Exocrine pancreatic dysfunction in malnourished Australian aboriginal children. Med J Aust. 1991;154:45-8.

9 Sandhyamoni S, Vijayakumari A, Balaraman Nair M. Bonnet monkey model for pancreatic changes in induced malnutrition. Pancreas 1999;18:84-95.

10 Pitchumoni CS. Pancreas in primary malnutrition disorders. Am J Clin Nutr 1973;26:374-9.

11 Crozier SJ, D'Alecy LG, Ernst SA, Ginsburg LE, Williams JA. Molecular mechanisms of pancreatic dysfunction induced by protein malnutrition. Gastroenterology 2009;137:1093-101.

12 Weisblum B, Herman L, Fitzgerald PJ. Changes in pancreatic acinar cells during proein deprivation. J Cell Biol 1962;12:313-27

13 Jahoor F, Badaloo A, Reid M, Forrester T. Protein metabolisim in severe childhood malnutrition. Ann Trop Paediatr 2008;28:87-101.

Table 1 Clinical profiles of SMID with acute pancreatitis

Patient	Age	Sex	Underlying disease	Respiratory care	Feeding methods	VPA therapy
1	4y	M	hypoxic-ischemic encephalopathy	oral suction	nasoduodenal tube	+
2	4y	F	sepsis-associated encephalopathy	tracheostomy, ventilator	nasogastric tube	-
3	17y	F	severe neonatal asphyxia	oral suction	nasoduodenal tube	-
4	9y	M	spinocerebellar degeneration	tracheostomy	gastrostomy	+
5	24y	M	Millar-Dieker syndrome	not required	oral feeding	-

Table 2 Comparison of clinical profiles between patients in the pancreatitis and control groups

	pancreatitis group	control group	*P* value
age (years)*	17 (4-29)	7 (4-28)	0.497
sex (male:female)*	0:3	8:5	0.054
respiratory medical care			
tracheostomy*	0/3 (0%)	1/13 (7.7%)	0.617
tracheostomy and ventilation*	1/3 (33%)	6/13 (46.1%)	0.304
NPPV*	0/3 (0%)	2/13 (15.4%)	0.466
only oral suction*	2/3 (66%)	2/13 (15.4%)	0.064
no respiratory medical care*	0/3 (0%)	2/13 (15.4%)	0.466
feeding method			
oral feeding*	1/3 (33%)	1/13 (7.7%)	0.231
nasogastric tube*	1/3 (33%)	5/13 (38.5%)	0.227
nasoduodenal tube*	1/3 (33%)	1/13 (7.7%)	0.509
gastrostomy*	0/3 (0%)	6/13 (46.2%)	0.093
valproic acid therapy	2/5 (40%)	2/15 (13.3%)	0.196

Values are expressed as median (percentage). Age ranges (years) are also provided.

NPPV: non-invasive positive pressure ventilation

*The parameters were compared after excluding patients medicated by VPA.

Table 3 Demographic and laboratory data in the pancreatitis and control groups

	AP Median (range)	Control Median (range)	*P*
Height (cm)	111.4 (105-141)	111.0 (85-161.5)	0.697
BW (kg)	24.6 (17.2-33)	16.0 (7.8-33.4)	0.201
BSA (m^2)	0.968(0.703-1.013)	0.710 (0.431-1.273)	0.542
BMI	15.6(12.3-26.5)	13.3 (9.5-20.9)	0.250
Daily calorie intake (kJ)	2512 (1172-4353)	1674 (1256-5023)	0.735
Daily calorie intake per BSA (kJ/m^2)	2594(1667-4298)	3264 (1769-5515)	0.741
Daily calorie intake per BW (kJ/kg)	76.2 (68.2-177.1)	131.0 (62.8-270.8)	0.276
T-Chol (mg/dl)	169 (122-240)	148 (98-196)	0.459
TG (mg/dl)	77 (23-425)	94 (30-300)	0.503
TP (g/dl)	5.2 (4.5-7.2)	7.2 (6.1-8.5)	0.079
Alb (g/dl)	2.4 (2.2-3.2)	4.2 (2.6-4.9)	0.026*

Parameters compared after excluding patients on VPA.
BW: body weight, BSA: body surface area, BMI: body mass index, T-Chol: total cholesterol,
TG: triglyceride, TP: total protein, Alb: Albumin