PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2004;10(22):3328-3331
World Journal of Gastroenterology
 ISSN 1007-9327

• CLINICAL RESEARCH •

Seasonal variation in the onset of acute pancreatitis

Massimo Gallerani, Benedetta Boari, Raffaella Salmi, Roberto Manfredini

Massimo Gallerani, Benedetta Boari, Roberto Manfredini, Section of Internal Medicine, Department of Clinical and Experimental Medicine, University of Ferrara, via Savonarola 9, I-44100 Ferrara, Italy
Raffaella Salmi, Department of Internal Medicine, St Anna Hospital, corso Giovecca 203, I-44100 Ferrara, Italy
Supported by a Research Grant "ex-60%" From the University of Ferrara
Correspondence to: Roberto Manfredini, Section of Internal Medicine, Department of Clinical and Experimental Medicine, University of Ferrara, via Savonarola 9, I-44100 Ferrara, Italy. mfr@unife.it
Telephone: +39-532-236817 **Fax:** +39-532-210884
Received: 2003-11-12 **Accepted:** 2004-02-24

Abstract

AIM: A circannual variation in the onset of several acute diseases, mostly dealing with cardiovascular system, has been reported. The present study was to verify the possible existence of a seasonal variability in the onset of acute pancreatitis.

METHODS: All patients consecutively admitted to the Hospital of Ferrara, Italy, between January 1998 to December 2002, whose discharge diagnosis was acute pancreatitis, were considered. According to the time of admission, cases were categorized into twelve 1-mo intervals and in four periods by season. χ^2 test for goodness of fit and partial Fourier series were used for statistical analysis.

RESULTS: During the study period, 549 cases of acute pancreatitis were observed. A significant peak of higher incidence was found in March-May, both for total population, males and subgroups with and without cholelithiasis or alcoholism. Fourier analysis showed the existence of a circannual rhythmic pattern with its main peak in March (95% C.L.: February-April, $P = 0.005$), and a secondary one in September. Death occurred more frequently in December-February, compared to the other periods ($P = 0.029$), and chronobiologic analysis yielded a seasonal peak in November-December ($P<0.001$).

CONCLUSION: This study shows the existence of a circannual variation in the onset of acute pancreatitis, with a significantly higher frequency of events in the spring, especially for patients with cholelithiasis or alcoholism. Moreover, events occurring during the colder months seem to be characterized by a higher mortality rate.

Gallerani M, Boari B, Salmi R, Manfredini R. Seasonal variation in the onset of acute pancreatitis. *World J Gastroenterol* 2004; 10(22): 3328-3331
http://www.wjgnet.com/1007-9327/10/3328.asp

INTRODUCTION

Many studies have shown a circannual variation in the onset of several diseases mostly dealing with cardiovascular system, characterized by an abrupt onset, e.g., fatal pulmonary embolism[1,2], ischemic and hemorrhagic stroke[3,4] and rupture of aortic aneurysms[5,6]. Seasonal specific patterns have also been reported for a series of miscellaneous diseases characterized by an acute onset, treated by the Emergency Department, including paralysis of cranial nerves[7], microcristalline arthritis[8], herpes zoster infection[9], epistaxis[10], urinary retention[11]. In the last few years several studies have investigated gastroenterologic diseases, and seasonal etiological patterns have been reported for the onset of peptic ulcer[12-15] and exhacerbation of inflammatory bowel diseases[16-18]. The aim of the present study was to determine by means of a validated chronobiological analysis, whether acute pancreatitis, a common but potentially harmful entity, might show a rhythmic seasonal variation as well.

MATERIALS AND METHODS

All cases of acute pancreatis (International Classification of Diseases, 9th Revision, Clinical Modification, ICD9-CM code: 577.0-8) consecutively observed from 1 January 1998 to 31 December 2002 at the St. Anna Hospital of Ferrara, Italy, were considered for the study. Ferrara is a small town in northern Italy particularly well suited for epidemiological studies. It has a stable population of approximately 150 000 inhabitants, almost exclusively white. The only available hospital in this community is St Anna Hospital, which also serves as the sole teaching center for the School of Medicine. The day and month of each event were categorized both into four 3-mo periods (according to seasons) and into twelve 1-mo intervals. Diagnosis was always made on the basis of clinical features, physical examination, laboratory data (serum amylase, isoamylase, lipase, and urinary amylase), and instrumental examinations, when necessary. For all subjects with acute pancreatitis the presence or absence of the two leading specific risk factors (alcoholism and biliary tract disease), was carefully investigated.

For statistical analysis, two different methods were used: χ^2 test for goodness of fit and partial Fourier series. To investigate possible differences in frequency peaks, χ^2 test for goodness of fit was applied to the total sample population and subgroups by gender, comparing observed against expected events during the four intervals season[19]. On the other hand, to verify the possible existence of a reproducible rhythmic pattern, cosinor analysis and partial Fourier series were applied to the time series, using specific commercially available software written for the Apple Macintosh computer[20]. The program allows, among all the possible combinations of the periods chosen by the user, the selection of the harmonic or the combination of harmonics that best explain the variance of data. The percentage of rhythms (PR: percentage of overall variability of data about the arithmetic mean attributable to the fitted rhythmic function) and the probability value resulting from the F statistic used to test the hypothesis of zero amplitude, were chosen to be reported in the results as representative parameters of goodness of fit and statistical significance of each fitted function, respectively. The program was used to calculate the midline estimating statistic of rhythm (MESOR: the rhythm-adjusted mean over the time period analyzed) and the amplitude (half the distance between the absolute maximum and minimum of the function) of the best-fitting-curve. The program was also used to calculate peak (ortophase) and trough (bathyphase) times of the fitted curves (times of occurrence of the absolute maximum and minimum) and the acrophase of each single harmonic change, together with the 95% confidence limits (CL). Significance

levels were always assumed for $P<0.05$. Conventional statistical analysis was performed using Student's *t* test for unpaired data. Significance levels were always set at $P<0.05$.

RESULTS

From January 1998 to December 2002, 549 consecutive cases of acute pancreatitis were observed, 285 cases were males (51.9%) and 264 were females (48.1%), their mean age was 65±17 years (difference between sexes $t = 2.7$, $P = 0.007$). Two hundred and eighty-six had cholelithiasis (52.1%) and 48 had chronic alcoholism (8.7%).

Deaths from acute pancreatitis were 18 (14 males and 5 females), accounting for 3.2%. Their mean age was 56±16 years,

Table 1 Monthly distribution of acute pancreatitis by gender and risk factors

Month	Total (*n* = 549)	Males (*n* = 285)	Females (*n* = 264)	Biliary tract disease (*n* = 286, 52.1%)	No bil. tract disease (*n* = 263, 48.9%)	Alcoholism (*n* = 48, 8.7%)	Fatal cases (*n* = 18, 3.2%)
January	34	18	16	17	17	1	3
February	46	19	27	22	24	2	2
March	62	35	27	28	34	8	1
April	61	33	28	31	30	7	0
May	56	32	24	35	21	5	0
June	44	23	21	19	25	3	0
July	40	20	20	23	17	2	1
August	45	25	20	30	15	4	1
September	39	20	19	22	17	4	1
October	40	20	20	19	21	2	2
November	46	25	21	22	24	6	3
December	36	15	21	17	19	3	4

Table 2 Seasonal distribution of acute pancreatitis (χ^2 test for goodness of fit)

	n (%)	December-February *n* (%)	March-May *n* (%)	June-August *n* (%)	September-November *n* (%)	χ^2	*P*
Total	549	116 (21.1)	179 (32.6)	129 (23.5)	125 (22.8)	17.5	0.001
Males	285 (51.9)	52 (18.2)	100 (35.1)	68 (23.9)	65 (22.8)	17.05	0.001
Females	264 (48.1)	64 (24.2)	79 (29.9)	61 (23.1)	60 (22.7)	3.55	0.316
Biliary tract disease	286 (52.1)	56 (19.5)	94 (32.8)	73 (25.4)	64 (22.3)	11.02	0.011
No bil. tract disease	263 (47.9)	60 (22.9)	85 (32.4)	56 (21.4)	61 (23.3)	7.93	0.049
Chronic alcoholism	48 (8.7)	6 (12.5)	20 (41.7)	10 (20.8)	12 (25)	8.67	0.035
Fatal cases	18 (3.2)	9 (50)	1 (5.6)	2 (11.1)	6 (33.3)	9.11	0.029

Table 3 Seasonal variation of acute pancreatitis (chronobiologic parameters by Fourier analysis)

	n	Period (h)	PR (%)	MESOR	Amplitude	Peak	95% CL	*P*
Total	549	8766	51.1			March	February-April	0.006
		4383	33.7			September	August-October	0.017
		Overall	84.8	45.68	3.28	March	February-April	0.005
Males	285	8766	42.6			March	February-April	0.030
		4383	32.7			September	NS	0.052
		Overall	75.4	23.71	9.06	March	February-April	0.027
Females	264	8766	50.9			March	February-April	0.024
		4383	22.3			September	NS	0.121
		Overall	73.3	21.97	4.52	March	February-April	0.035
Biliary tract disease	286	8766	42.2			March	NS	0.074
		4383	19.5			August	NS	0.234
		Overall	61.8	23.72	7.60	March	NS	0.108
No bil. tract disease	263	8766	44.8			March	February-April	0.041
		4383	25.1			October	NS	0.119
		Overall	69.9	21.96	7.66	March	NS	0.052
Chronic alcoholism	48	8766	13.2			March	NS	0.415
		4383	40.7			September	NS	0.109
		Overall	53.9	3.91	2.51	March	NS	0.192
Fatal cases	18	8766	86.2			November	November-December	<0.001
		4383	10.9			June	May-July	0.004
		Overall	97.1	1.50	1.90	November	November-December	<0.001

PR = percentage of rhythm (percentage of overall variability of data about arithmetic mean attributable to the rhythmic fitted function MESOR = midline estimated statistics of rhythm, the rhythm-adjusted mean over the time period analysed amplitude: half the distance between the absolute maximum and minimum of the function of the best-fitting curve 95% CL = 95% confidence limits NS = not significant, (when acrophase did not reach the significance level, 95% CL could not be given).

significantly lower than that of survived subjects (65±17 years, $t = 2.20$, $P = 0.028$). Among the subgroups of fatal events, 3 had gallstones (16.6%, $\chi^2 = 1.91$ $P = 0.178$), and 4 had chronic alcoholism (22.2%, $\chi^2 = 3.78$ $P = 0.075$). Table 1 shows the monthly distribution by gender, and subgroups by risk factors. A peak of higher frequency of events was found in the period March-May for the total samples and in particular for males and subgroups of subjects with and without gallstones and chronic alcoholism (Table 2). The percentage of fatal events was significantly higher in December-February ($n = 9$, 17.3% of acute pancreatitis observed in that period, 50% of total deaths, $\chi^2 = 9.11$, $P = 0.029$, compared to the other periods).

Chronobiologic analysis (Table 3) showed the existence of a circannual rhythmic variation characterized by a main peak in March (PR 84.8, 95% CL: February-April, $P = 0.005$), and a secondary peak in September. This pattern was confirmed also for subgroups by gender (men: PR 75.4, 95% CL: February-April, $P = 0.027$), and (women: PR 73.3, 95% CL: February-April, $P = 0.035$). Moreover, a highly significant peak was noticed for fatal cases in late November (PR 97.1, 95% CL: October-December, $P<0.001$). NO statistically significant trend for a peak in March was found for subgroups of subjects with or without cholelithiasis (respectively: PR 61.8, 95% CL: February-April, $P = 0.109$; and PR 69.9, 95% CL: February-April, $P = 0.052$).

DISCUSSION

Identification of patients with acute pancreatitis is important due to the increased risk of death.

To our knowledge, there was only one recent study in medical literature, which aimed to evaluate the seasonal variation in the onset of acute pancreatitis[20]. In a total of 263 cases observed for a period of 9 years in a German hospital, no correlation between admissions and a specific month or season was found, other earlier reports were mostly hypotheses[21,22]. Our study instead showed a clear seasonal variation in the onset of acute pancreatitis characterized by a higher frequency in the spring, with a maximum in March-May. This pattern was particularly evident for patients with cholelithiasis and chronic alcoholism. It is difficult to give an exhaustive explanation for such a temporal pattern. Seasonal and circannual patterns have been reported for the prevalence of *Helicobacter pylori* infection[14], or for relapses of inflammatory bowel disease for hospital admissions[15,23].

As for circadian aspects, some acute dramatic clinical events, e.g., variceal and gastrointestinal bleeding[24-26] showed obvious circadian patterns. Daily variations of some biologic functions have also been found as possible co-factors in several gastrointestinal diseases, e.g., fibrinolysis in liver cirrhosis and esophageal varices[27], electrical uncoupling and ectopic pacemaker activity in intestinal motor dysfunction[28], melatonin and duodenal ulcer[29,30], colonic motility in diverticular disease[31] and rectal motor activity in constipation[32].

At present we do not know enough about seasonal biological changes potentially affecting onset of acute pancreatitis, e.g., secretion of pancreatic enzymes, biliary acids. However, it is possible that variations in physiological functions with seasonal change may be associated with an increased risk of pancreatitis. Oxygen free radicals, for example, were known to be a meaningful index for the severity of pancreatitis[33], but possible variations in free radical generation have not been investigated yet. Our results seemed to be able to identify a higher mortality for colder months (November-December). This is particularly interesting when considering that both the mean age of subjects and the incidence of risk factors (gallstones, alcoholism) in the subgroup of fatal cases were significantly lower compared with those in the subgroup of non fatal events. Thus, it seems that acute events of pancreatitis occurring in the colder months may be more at risk in terms of severity and mortality. Further studies conducted on larger samples and addressed to other countries of different latitudes would be needed.

ACKNOWLEDGEMENTS

The authors thank Mr. Franco Guerzoni, from the Statistical Service of Ferrara St Anna Hospital, for his helpful assistance in collection of cases and analysis of data.

REFERENCES

1 **Gallerani M,** Manfredini R, Ricci L, Grandi E, Cappato R, Calo G, Pareschi PL, Fersini C. Sudden death from pulmonary thromboembolism: chronobiological aspects. *Eur Heart J* 1992; **13**: 661-665
2 **Manfredini R,** Gallerani M, Salmi R, Zamboni P, Fersini C. Fatal pulmonary embolism in hospitalized patien: evidence for a winter peak. *J Int Med Res* 1994; **22**: 85-89
3 **Gallerani M,** Trappella G, Manfredini R, Pasin M, Napolitano M, Migliore A. Acute intracerebral haemorrhage: circadian and circannual patterns of onset. *Acta Neurol Scand* 1994; **89**: 280-286
4 **Gallerani M,** Portaluppi F, Maida G, Chieregato A, Calzolari F, Trapella G, Manfredini R. Circadian and circannual rhythmicity in the occurrence of subarachnoid hemorrhage. *Stroke* 1996; **27**: 1793-1797
5 **Manfredini R,** Portaluppi F, Salmi R, Zamboni P, la Cecilia O, Kuwornu Afi H, Regoli F, Bigoni M, Gallerani M. Seasonal variation in the occurrence of nontraumatic rupture of thoracic aorta. *Am J Emerg Med* 1999; **17**: 672-674
6 **Mehta HR,** Manfredini R, Hassan F, Sechtem U, Bossone E, Oh JK, Cooper JV, Smith DE, Portaluppi F, Penn M, Hutchison S, Nienaber CA, Isselbacher EM, Eagle KA. Chronobiological patterns of acute aortic dissection. *Circulation* 2002; **106**: 1110-1115
7 **Gallerani M,** Delli Gatti C, Salmi R, Kuwornu Afi H, la Cecilia O, Manfredini R. Seasonal variations in the incidence of cranial nerve paralysis. *J Int Med Res* 1999; **27**: 130-133
8 **Gallerani M,** Govoni M, Mucinelli M, Bigoni M, Trotta F, Manfredini R. Seasonal variation in the onset of acute microcrystalline arthritis. *Rheumatology* 1999; **38**: 1003-1006
9 **Gallerani M,** Manfredini R. Seasonal variation in herpes zoster infection. *Br J Dermatol* 2000; **142**: 588-589
10 **Manfredini R,** Gallerani M, Portaluppi F. Seasonal variation in the occurrence of epistaxis. *Am J Med* 2000; **108**: 759-760
11 **Braverman DZ,** Morali GA, Patz JK, Jacobsohn WZ. Is duodenal ulcer a seasonal disease? A retrospective endoscopic study of 3105 patients. *Am J Gastroenterol* 1992; **87**: 1591-1593
12 **Tivon K,** Cohen P. Seasonality in duodenal ulcer disease: possible relationship with circannually cycling neurons enclosed in the biological clock. *Am J Gastroenterol* 1995; **90**: 1189-1190
13 **Thomopoulos KC,** Katsakoulis EC, Margaritis VG, Mimidis KP, Vagianos CE, Nikolopoulou VN. Seasonality in the prevalence of acute upper gastrointestinal bleeding. *J Clin Gastroenterol* 1997; **25**: 576-579
14 **Raschka C,** Schorr W, Koch HJ. Is there seasonal periodicity in the prevalence of *Helicobacter pylori*? *Chronobiol Int* 1999; **16**: 811-819
15 **Sonnenberg A,** Jacobsen SJ, Wasserman IH. Periodicity of hospital admissions for inflammatory bowel disease. *Am J Gastroenterol* 1994; **89**: 847-851
16 **Moum B,** Aadland E, Ekbom A, Vatn MH. Seasonal variations in the onset of ulcerative colitis. *Gut* 1996; **38**: 376-378
17 **Zeng L,** Anderson FH. Seasonal change in the exacerbations of Crohn's disease. *Scand J Gastroenterol* 1996; **31**: 79-82
18 **Ott L,** Memdenhall W, Larson R. Statistical test of hypotheses: the one sample case. In: Statistics. Boston , MA: *Duxbury Press* 1978: 242-246
19 **Mojon A,** Fernandez JR, Hermida RC. Chronolab: an interactive software package for chronobiologic time series analysis written for the Macintosh computer. *Chronobiol Int* 1992; **9**: 403-412
20 **Lankisch PG,** Assmus C, Pflichthofer D. The calendar and acute pancreatitis. *Pancreas* 1998; **16**: 465-467
21 **Poikolainen K.** Seasonality of alcohol-related hospital admis-

sions has implications for prevention. *Drug Alcohol Depend* 1982; **10**: 65-69
22 **Reimann HA.** Letter: Three periodic diseases as causes of recurrent abdominal pain in childhood. *Arch Dis Child* 1976; **51**: 244
23 **Minoli G,** Imperiali G, Colombo E, De Franchis R, Mortara G, Prada A, Rocca F. Biphasic annual periodicity in relapses of inflammatory bowel diseases. Gruppo di studio per le malattie infiammatorie intestinale. *J Clin Gastroenterol* 1995; **21**: 27-29
24 **Manfredini R**, Gallerani M, Salmi R, Calo G, Pasin M, Bigoni M, Fersini C. Circadian variation in the time of onset of acute gastrointestinal bleeding. *J Emerg Med* 1994; **12**: 5-9
25 **Siringo S,** Bolondi L, Sofia S, Hermida RC, Gramantieri L, Gaiani S, Piscaglia F, Carbone C, Misitano B, Corinaldesi R. Circadian occurrence of variceal bleeding in patients with liver cirrhosis. *J Gastroenterol Hepatol* 1996; **11**: 1115-1120
26 **Mann NS,** Hillis A, Mann SK, Buerk CA, Prasad VM. In cirrhotic patients variceal bleeding is more frequent in the evening and correlates with severity of liver disease. *Hepatogastroenterology* 1999; **46**: 391-394
27 **Piscaglia F,** Siringo S, Hermida RC, Legnani C, Valgimigli M, Donati G, Palareti G, Gramantieri L, Gaiani S, Burroughs AK, Bolondi L. Diurnal changes of fibrinolysis in patients with liver cirrhosis and esophageal varices. *Hepatology* 2000; **31**: 349-357
28 **Der T,** Bercik P, Donnelly G, Jackson T, Berezin I, Collins SM, Huizinga JD. Interstitial cells of cajal and inflammation-induced motor dysfunction in the mouse small intestine. *Gastroenterology* 2000; **119**: 1590-1599
29 **Malinovskaya N,** Komarov FI, Rapoport SI, Voznesenskaya LA, Wetterberg L. Melatonin production in patients with duodenal ulcer. *Neuroendocrinol Lett* 2001; **22**: 109-117
30 **Kato K,** Murai I, Asai S, Takahashi Y, Nagata T, Komuro S, Mizuno S, Iwasaki A, Ishikawa K, Arakawa Y. Circadian rhythm of melatonin and prostaglandin in modulation of stress-induced gastric mucosal lesions in rats. *Aliment Pharmacol Ther* 2002; **16**(Suppl 2): 29-34
31 **Bassotti G,** Battaglia E, Spinozzi F, Pelli MA, Tonini M. Twenty-four hour recordings of colonic motility in patients with diverticular disease: evidence for abnormal motility and propulsive activity. *Dis Colon Rectum* 2001; **44**: 1814-1820
32 **Rao SS,** Sadeghi P, Batterson K, Beaty J. Altered periodic rectal motor activity: a mechanism for slow transit constipation. *Neurogastroenterol Motil* 2001; **13**: 591-598
33 **Park BK,** Chung JB, Lee JH, Suh JH, Park SW, Song SY, Kim H, Kim KH, Kang JK. Role of oxygen free radicals in patients with acute pancreatitis. *World J Gastroenterol* 2003; **9**: 2266-2269

Edited by Wang XL **Proofread by** Xu FM