

Etiological Factors of Non Alcohol Non Gallstone Related Acute Pancreatitis: A Cross sectional hospital based study from Medical College and Hospital, Kolkata, West Bengal

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This title is indexed in **SciVerse Scopus**



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Original Article

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Abstract

Background

Gall stone diseases and alcohol are the two most common causes of acute pancreatitis. The present work was undertaken to identify the various etiological factors in acute pancreatitis after excluding alcoholism and gall stone diseases. The etiology of an attack of non alcohol non gall stone acute pancreatitis is highly variable. The main objective was to identify the causing factor, because it can have an effect on the specific treatment of acute pancreatitis. This is a rare cross- sectional study of its kind

Nepal Journal of Epidemiology 2014; 4(3): 351-62 Copyright © 2014 CEA& INEA Published online by NepJOL-INASP www.nepjol.info/index.php/NJE



which is the first one to be reported from India.

Materials and Methods

A cross-sectional community based study was designed and conducted in Medical College and Hospital, Kolkata, West Bengal, India from July 2009 to June 2011. Z test and Chi square test were used to observe the variation between different variables and strength of the relationship with logistic regression. Odd ratios were calculated and their 95% confidence intervals (95% Cl). p < 0.05 was considered as statistically significant.

Results

CMV was the commonest etiology of non alcohol and non gallstone acute pancreatitis 26.7% followed by HEV 6.7% and Pancreas Divisum 6.7%%, SOD 3.3%, EBV 3.3%, Mumps 3.3%, Hepatitis 3.3%, Tumour 3.3%, Choledochal cyst 3.3%,Drugs 3.3% and Gallstone 3.3%. Logistic regression analysis finding indicates that acute pancreatitis was found more prevalent in < 40 yrs [OR 2.076,95%(CI 0.339, 12.716)] and among patients having monthly income of <5000 rs/month yrs [OR 1.4,95%(CI 0.224, 8.768)]. According to the severity of CT grading, Patients had Grade D severity [OR 2.667,95%(CI 0.158, 45.141)], Grade C[OR 1.333,95%(CI 0.104, 17.098)] and Grade E [OR 1.333,95%(CI 0.88, 20.108)]as compared to Grade B severity of CT.

Conclusion

In the study an etiological factor was evident among almost 3/4th of the patients of non-alcoholic and non-gallstone pancreatitis. The most common etiological factors were CMV followed by HEV. These results rather suggests that the most diligent workup including a biliary microcrystal analysis, a sphincter of Oddi manometry and possible gene analysis for hereditary disorders may further reduce the apparently idiopathic group in the analysis of such patients.

Keywords: CMV, HEV, Acute pancreatitis, West Bengal

Background

Acute pancreatitis is a potentially lethal condition resulting from an acute inflammatory process in the pancreas usually manifested by upper abdominal pain and raised concentration of pancreatic enzymes in blood, urine, peritoneal fluid at least 3 times the normal ¹. If the cause of the attack can be eliminated no further attacks may ensue². In 1963, a symposium on pancreatitis was held in Marseille in France and pancreatitis was divided into acute and chronic types: relapsing and non-relapsing varieties³. The essential difference between acute and chronic pancreatitis is the presence of permanent and progressive morphologic or functional damage in the latter. The major drawback of Marseille classification is the frequent inability to distinguish acute and chronic forms of the disease based on clinical presentation. It is for this reason that after an acute attack of pancreatitis, it is important to look for predisposing factors of these episodes of acute

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pancreatitis and eliminate the possible causes and reverse the susceptibility.

Gall stone diseases⁴ and alcohol ⁵ are the most common causes behind acute pancreatitis, the former ranging from 30-70% as a cause and the latter averaging about 30% incidence⁶. Once these two causes are excluded there remains a group, approximately 20-25%, and in this context other predisposing factors like structural or functional alterations in the ductal system, microlithiasis, metabolic defects, Infections, trauma , hereditary and iatrogenic causes obstruction, unknown causes, drugs , auto-immunity infections , post-operative, post-ERCP, trauma, hypertriglyceridemia and genetic factors may be associated with acute pancreatitis^{7, 8}.

The present work was undertaken to identify the various etiological factors which were responsible for acute pancreatitis after excluding alcoholism and gall stone diseases. The etiology attack which is associated with non alcohol and non gall stone acute pancreatitis is highly variable. The main objective was to identify the causing factor because it can have an effect on the specific treatment of acute pancreatitis. Furthermore, in some cases relapses of acute pancreatitis can be prevented by eliminating the causing factor. The specific objectives were to find the socio demographic factors, radiological, serological and biochemical and miscellaneous factors associated with acute pancreatitis. This study is a rare cross sectional study and is the first study reported from India. The need of the study also arises from the fact that there are no sufficient data related to the etiology of non gallstone and non alcoholic acute pancreatitis in India and SAARC region in particular and worldwide in general.

Material and Methods

Study design and the participants:

A cross-sectional community based study was designed and conducted in the Medical College and Hospital, Kolkata, West Bengal, India.

Data collection:

The study was conducted for a period of 2 years from July 2009 to June 2011.

Inclusion criteria:

Patients with classical symptoms of acute pancreatitis like pain abdomen, rise in serum amylase >3 times the normal/Ultrasonography/CECT findings(optional) consistent with diagnosis of acute pancreatitis were included in the study.

Exclusion criteria:

Patients with history of alcoholism, Cholelithiasis/ choledocholithiasis on Ultrasonography abdomen, previous ERCP for stenting of pancreatic duct were excluded from the study.



Sample size calculation:

For 95% confidence interval and, significance level α = 5%, P = 70%, Q = 30%, allowable error = 10%, required sample size was 165. P = percentage of etiological factors identified among patients with acute pancreatitis Prior to the study, the pilot study was conducted among 10 patients and subsequently it was found that 70% patients were having a etiological factor in non-alcoholic and non gall stone acute pancreatitis. Over 30 sample sizes were selected for a period of 2 years of duration as this is a rare cross sectional study. Most of the cases of acute pancreatitis are associated with alcohol and gall stone. The research aims at determining the etiology of nonalcohol and non gall stone acute pancreatitis⁹.

Outcome Variable:

The main outcome variable was to find the various etiological factors associated with non alcoholic and non gall stone acute pancreatitis like CMV, SOD, EBV, Mumps, Hepatitis, Tumour, Choledochal cyst, Pancreas Divisum, Drugs, Gallstone and None.

Explanatory variables:

Various socio-demography related details of patients namely Age, Gender, Monthly Income, marital status, Religion and Education were taken into consideration. History of previous attacks of acute pancreatitis, recurrence and total number of attacks of acute pancreatitis, follow ups, various biochemical parameters like LFT, ALP, Sweat Chloride test, CECT abdomen, USG Abdomen, MRCP, ERCP, Serological investigations like CMV and EBV were also considered.

Ethical committee approval:

All investigations and invasive procedures that were administered to the patients of acute pancreatitis involve no risk of morbidity and mortality to the subjects. The procedures used in this study were explained in detail to the participating patients and informed consent was taken from them. The patient reserved the right to withdraw from the study at any stage without any bias to their evaluation and treatment. The Research was conducted in accordance to the latest version of the Declaration of Helsinki. Prior to the study, ethical committee approval was obtained from the institutional ethical committee of Medical college and hospital, Kolkata, India.

Data management and statistical analysis:

The data collected was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and EPI Info 3.5.1 Windows Version. Z test and Chi square test were used to observe the difference between different variables and strength of the relationship with logistic regression. Odds ratios were calculated and their 95% confidence intervals (95% CI). p < 0.05 was considered as statistically significant¹⁰.

Non gallstone and non alcoholic acute pancreatitis Result:

Socio demographic factors and etiology

Most of the patients were <40 yrs 63.3%, male 63.3%, Muslim 56.7% followed by Hindu 43.3%, Married 76.7%, education level less than matriculation 83.3%, monthly income <5000/month 70% (Table 1). Etiological factors were found in 66.7% of the subjects. Among the etiological factors the most common cause were CMV 26.7% followed by HEV 6.7% and Pancreas Divisum 6.7%%, SOD 3.3%, EBV 3.3%, Mumps 3.3%, Hepatititis 3.3%, Tumour 3.3%, Choledochal cyst 3.3%,Drugs 3.3% and Gallstone 3.3% respectively.

Socio d	emographic fac Factors	tors	P value	95% CI
Age	>40 yrs	11(36.7)	0.0384 6 †	[19.45 <i>,</i> 53.95]
	< 40 yrs	19(63.3)		[46.05, 80.55]
Gender	Female	11(36.7)	0.0384 6 †	[19.45 <i>,</i> 53.95]
	Male	19(63.3)		[46.05, 80.55]
Education	>Matriculat ion	5(16.7)	0.0000 1†	[3.35, 30.05]
	< Matriculati on	25(83.3)		[69.95 <i>,</i> 96.65]
Monthly Income	>5000/mon th	9(30)	0.0019 4†	[13.6, 46.4]
	<5000/mon th	21(70)		[53.6, 86.4]
Religion	Hindu	13(43.3)	0.30x	[25.57 <i>,</i> 61.03]
	Muslim	17(56.7)		[38.97 <i>,</i> 74.43]
Marital Status	Unmarried	7(23.3)	0.0000 1 ⁺	[8.17, 38.43]
	Married	23(76.7)		[61.57 <i>,</i> 91.83]

Table 1: Socio demographic factors of Acute Pancreatitis

*p<0.05, statistically significant, p>0.05, statistically not significant

Radiological Investigations

According to the findings of USG abdomen in acute pancreatitis with CMV, sludge and fatty liver was found in 25% cases in each categories. Sludge was found in SOD, hepatitis showed fatty liver, Tumour showed SVT and IHBRD and Choledochal cyst was found as associated findings. In CT grading of CMV, 37.5% of the subjects were having Grade C severity followed by Grade D 25% and Grade E 25% respectively. In SOD Grade E 100%, mumps Grade B in 100%, Hepatitis, Choledochal cyst and Tumour Grade E, Pancreas divisum showed Grade C 50% and Grade B 50% severity. In CECT abdomen gall stone was diagnosed in 1 case.

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Table –2: Etiological factors and various Radiological investigations of Acute Pancreatitis

Radi	ological tigations	Etiological factors of acute Pancreatitis											
		SOD n=1(3. 3%)	EBV n=1(3.3%	Mum ps n=1(HEV n=2(6.7 %%)	CMV n=8 (26.7%)	Hepatiti tis n=1(3.3	Tumour n=1(3.3%)	Choledo chal cyst n=1(3.3	Pancreas Divisum n=2(6.7%	Drugs n=1 (3.3%)	Gallstone n=1 (3.3%)	None N=10 (33.3%)
Findings of USG	Thickned gall bladder	0(0)	0(0)	3 3% 0(0)	0(0)	0(0)	%) 0(0)	0(0)	%) 0(0)	%) 0(0)	0(0)	1(100)	0(0)
Abdomen	SVT & IHBRD	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)
	Choledochal cyst	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)
	Fatty Liver	0(0)	0(0)	0(0)	2(100)	2(25)	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)	1(10)
	Sludge	1(100)	0(0)	0(0)	0(0)	2(25)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	None	0(0)	1(10 0)	1(10 0)	0(0)	4(50)	0(0)	0(0)	0(0)	2(100)	1(100)	0(0)	9(90)
	P value					0.0	000+						
CT Grading	Grade B	0(0)	0(0)	1(10 0)	0(0)	1(12.5)	0(0)	0(0)	0(0)	1(50)	0(0)	0(0)	2(20)
of Severity	Grade C	0(0)	1(10 0)	0(0)	0(0)	3(37.5)	0(0)	0(0)	0(0)	1(50)	1(100)	1(100)	6(60)
of Acute Pancreati	Grade D	0(0)	0(0)	0(0)	1(50)	2(25)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(20)
tis	Grade E	1(100)	0(0)	0(0)	1(50)	2(25)	1(100)	1(100)	1(100)	0(0)	0(0)	0(0)	0(0)
	P value					0.	561 ^x						
CECT Abdomen	Gallstone	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)
associate d findings	Choledochal Cyst	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)
	None	1(100)	1(10 0)	1(10 0)	8(100)	1(100)	1(100)	0(0)	2(100)	1(100)	1(100)	0(0)	10(100)
	P value					0.	.001†						
ERCP Structura	Delayed Excretion	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
l Defects	Pancreas Divisum	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(100)	0(0)	0(0)	0(0)
	Stricture of main pancreatic	0(0)	1(10 0)	0(0)	1(50)	1(12.5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	None	0(0)	0(0)	1(10 0)	1(50)	7(87.5)	1(100)	1(100)	1(100)	0(0)	1(100)	1(100)	10(100)
	P value					0.0	000+						
MRCP Structura	Choledochal cyst	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)
l Defects	Pancreatic Mass	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	0(0)
	Pancreas Divisum	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	2(100)	0(0)	0(0)	0(0)
	None	1(100)	1(10 0)	1(10 0)	2(100)	8(100)	1(100)	0(0)	0(0)	0(0)	1(100)	1(100)	10(100)
	P value					0.	000+						

⁺p<0.05, statistically significant,

× p>0.05, statistically not significant

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Table 3: Biochemical and Serological Investigations of Acute Pancreatitis

Biochem Serologic		Etiological factors of acute Pancreatitis											
		SOD n=1(3. 3%)	EBV n=1 (3.3%)	Mu mps n=1(3 .3%	HEV n=2(6.7 %%)	CMV n=8 (26.7%)	Hepatititis n=1(3.3%)	Tumour n=1 (3.3%)	Choled ochal cyst n=1(3.	Pancreas Divisum n=2(6.7% %)	Drugs n=1 (3.3%)	Gallstone n=1 (3.3%)	None N=10 (33.3%)
Serum Amylase	Normal	0(0)	0(0)	0(0)	0(0)	2(25)	1(100)	1(100)	0(0)	1(50)	0(0)	0(0)	1(10)
level	Elevated > 3 times Normal	1(100)	1(100)	1(10 0)	2(100)	6(75)	0(0)	0(0)	1(100)	1(50)	1(100)	1(100)	9(90)
	P value					(0.373 ^x						
Sweat Test	25- 40mEq/lit	1(100)	0(0)	0(0)	2(100)	2(25)	2(25)	0(0)	1(100)	0(0)	1(100)	1(100)	2(20)
	41-55 mEq/liter	0(0)	1(10 0)	1(10 0)	0(0)	6(75)	6(75)	1(100)	0(0)	2(100)	0(0)	0(0)	8(80)
	P value					0.	119 ^x						
ALP	Abnormal	1(100)	1(10 0)	0(0)	1(50)	0(0)	0(0)	0(0)	1(100)	1(50)	0(0)	0(0)	2(20)
	Normal	0(0)	0(0)	1(10 0)	1(50)	8(100)	1(100)	1(100)	0(0)	1(50)	1(100)	1(100)	8(80)
	P value					0.	162 ^x						
LFT	Normal	0(0)	0(0)	0(0)	1(50)	5(62.5)	0(0)	1(100)	0(0)	0(0)	0(0)	1(100)	4(40)
	Abnormal	1(100)	1(10 0)	1(10 0)	1(50)	3(37.5)	1(100)	0(0)	1(100)	2(100)	1(100)	0(0)	6(60)
	P value					0.5	521 ^x						
HEV Seropositiv	Positive	0(0)	0(0)	0(0)	2(100)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
ity	Negative	1(100)	1(10 0)	1(10 0)	0(10)	8(100)	6(100)	1(100)	1(100)	2(100)	1(100)	1(100)	10(100)
	P value					0.00)2†						
CMV Seropositiv ity	Positive	0(0)	0(0)	0(0)	2(100)	8(100)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
	Negative	1(100)	1(10 0)	1(10 0)	0(10)	0(0)	6(100)	1(100)	1(100)	2(100)	1(100)	1(100)	10(100)
	P value					0.0	02†						

+p<0.05, statistically significant
× p>0.05, statistically not significant



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Table 4: Association of Miscellaneous factors and acute pancreatitis

Miscellan	eous factors						Etiological fac	ctors of acute	Pancreatit	is			
		SOD n=1(3. 3%)	EBV n=1(3.3%)	Mum ps n=1(3 .3%)	HEV n=2(6.7 %%)	CMV n=8 (26.7%)	Hepatititis n=1(3.3%)	Tumour n=1(3.3%)	Choled ochal cyst n=1(3.3 %)	Pancreas Divisum n=2(6.7% %)	Drugs n=1 (3.3%)	Gallstone n=1 (3.3%)	None N=10(33. 3%)
Prior/ Number	> 3 attacks	0(0)	0(0)	0(0)	1(50)	2(25)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	4(40)
of attacks of acute	< 3 attacks	1(100)	1(10 0)	1(10 0)	1(50)	6(75)	1(100)	1(100)	0(0)	2(100)	1(100)	1(100)	6(60)
pancreati tis	P value						0.7	57 [×]					
Recurren ce of	> 1 episode	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	3(30)
attacks during	< 1 episode	1(100)	1(10 0)	1(10 0)	2(100)	8(100)	1(100)	1(100)	1(100)	2(100)	1(100)	1(100)	7(70)
period of evaluatio	P value		- ,	- ,			0.8	25 [×]					
Total Number	> 3 attacks	0(0)	1(10 0)	0(0)	2(100)	2(25)	0(0)	0(0)	1(100)	0(0)	0(0)	1(100)	4(40)
of attacks of acute	< 3 attacks	1(100)	0(0)	1(10 0)	0(0)	6(75)	1(100)	1(100)	0(0)	2(100)	1(100)	0(0)	6(60)
pancreati tis t	P value						0.2	28 [×]					
Comtplic	Infected Necrosis	0(0)	0(0)	0(0)	1(50)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
ations of acute	Abscess	0(0)	0(0)	0(0)	0(0)	1(12.5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(10)
Pancreati tis	Pseudocyst	0(0)	0(0)	0(0)	0(0)	2(25)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(10)
us	None	1(100)	1(10 0)	1(10 0)	1(50)	5(62.5)	1(100)	1(100)	1(100)	2(100)	1(100)	1(100)	8(80)
	P value		0)	01			0.9	71 [×]					
Follow up	< 12 month	0(0)	0(0)	0(0)	2(100)	5(62.5)	1(100)	1(100)	0(0)	0(0)	0(0)	1(100)	2(20)
	>12 month	1(100)	1(10 0)	1(10 0)	0(0)	3(37.5)	0(0)	0(0)	1(100)	2(100)	1(100)	0(0)	8(80)
	P value	0.16 ^x											
Total number	2	0(0)	1(10 0)	0(0)	1(50)	3(37.5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
of Diagnosis	1	1(100)	0(0)	1(10 0)	1(50)	5(62.5)	1(100)	1(100)	1(100)	2(100)	1(100)	1(100)	0(0)
based on etiologica	None	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	10(100)
l factors	P value							0.008†					

⁺p<0.05, statistically significant

 \times p>0.05, statistically not significant



50 % of the subjects showed stricture of main pancreatic duct in ERCP, delayed excretion in SOD, stricture of main pancreatic duct in EBV, pancreas divisum in all cases of pancreas divisum. In MRCP, pancreatic mass, choledochal cyst and pancreas divisum was found (Table 2).

Biochemical and Serological investigations

Serum Amylase was raised > 3 times normal in 80 % of the subjects. In CMV, Serum Amylase was raised > 3 times normal in 75% of the cases, whereas serum amylase was elevated in all cases of SOD, EMV,mumps, HEV, choledochal cyst, drugs, gallstone. It was not elevated in 100% subjects of Tumour, hepatitis100 %, pancreas divisum 50% cases and in 25% cases of CMV. Sweat Chloride test value was within normal ranges. ALP levels were abnormal in SOD 100%, EBV 100%, Choledochal cyst100% subjects. In CMV, ALP was normal in all cases. LFT was normal in 62.5% cases of CMV, whereas LFT was found to be abnormal in SOD, EBV, mumps, hepatitis, choledochal cyst and drugs.

As far as the serological findings were concerned, HEV seropositivity was seen in only 2 cases of acute pancreatitis whereas CMV seropositivity were evident in 8 cases (Table 3).

 Table 5: Logistic Regression Table of Socio demographic

 factors and acute Pancreatitis

Socio dem Facto	Cyto Megalo Virus (CMV)				
Age	> 40 yrs	1			
~ <u>6</u> c	<40 yrs	2.076 (0.339, 12.716)x			
Gender	Female	1			
Gender	Male	0.952(0.179, 5.081)x			
	> Matriculation	1			
Education	<matriculation< td=""><td>0.474(0.63, 3.538)x</td></matriculation<>	0.474(0.63, 3.538)x			
Religion	Hindu	1			
	Muslim	0.692(0.136, 3.518)x			
Marital Status	Unmarried	1			
	Married	-			
	>5000/month	1			
Monthly Income	<5000/month	1.4(0.224, 8.768)x			

× p>0.05, statistically not significant

- P value cannot calculate

Miscellaneous findings

The majority of patients were having prior attacks of acute pancreatitis < 3 attacks which was found in 73.3% of cases. In CMV with acute pancreatitis 75% of the subjects were having < 3 prior attacks, > 3 prior attacks were found in 50% cases of HEV and in all cases of choledochal cyst 100%. Recurrence of attack < 1 during evaluation occurred in most of the cases 90%. Total number of attacks > 3 occurred in all

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Non gallstone and non alcoholic acute pancreatitis

cases of EBV, HEV, gallstone and in 25 % of cases of CMV. Complication of Acute Pancreatitis such as infected necrosis was found in HEV, whereas in CMV there were Pseudocyst in 25% of cases and abscess in 12.5% cases.Follow up of patients were > 12 months in 60% of cases. Follow up > 12 months was done in SOD, HBV, mumps, choledochal cyst, pancreas divisum and in 37.5% of cases of CMV. As per as the total number of diagnosis based on etiological factors were concerned most of the patient was diagnosed as none 50% cases , followed by single etiology 33.3% cases and multiple etiologies 16.7 % of patients(Table 4).

Determinants of etiological factors and acute pancreatitis by logistic regression

Logistic regression analysis finding shows that acute pancreatitis was found more prevalent in < 40 yrs [OR 2.076,95 %(CI 0.339, 12.716)] as compared to > 40 yrs and to the patients who were having monthly income of <5000 rs/month yrs [OR 1.4,95%(CI 0.224, 8.768)] as compared to monthly income > 5000 rs/month (Table 5).

Table 6: Logistic Regression Analysis of Investigations andHistory of patients of acute pancreatitis

Investigations	and History of pa pancreatitis	tients of acute	Cyto Megalo Virus (CMV)
			Odds Ratio
History of acute	Prior/ No attacks of	> 3 attacks	1
pancreatitis	acute pancreatitis	< 3 attacks	1.125(0.176, 7.191) x
	Total no. of	> 3 attacks	1
	attacks of acute pancreatitis	< 3 attacks	2.077(0.339, 12.716) x
	Follow up	< 12 months	1
		> 12 months	0.28 (0.52, 1.516) x
Biochemical		Normal	1
Parameters	Serum Amylase	Elevated >3 times Normal	0.667 (0.097, 4.6) x
	LFT	Normal	1
		Abnormal	0.28(0.052, 1.516) x
	Sweat Chloride test	25-40	1
		41-55	2.077 (0.339, 12.716) x
	CT Grading	Grade B	1
		Grade C	1.333(0.104, 17.098) x
Investigations		Grade D	2.667(0.158, 45.141) x
		Grade E	1.333(0.88, 20.108) x

× p>0.05, statistically not significant



So far as the history taking and investigations are concerned, patients [OR 2.077,95%(CI 0.339, 12.716)] have a tendency of having total number of attacks < 3 attacks as compared to > 3 attacks. According to the severity of CT grading, Patients were reported to have Grade D severity [OR 2.667,95%(CI 0.158, 45.141)], Grade C[OR 1.333,95%(CI 0.104, 17.098)] and Grade E [OR 1.333,95%(CI 0.88, 20.108)]as compared to Grade B severity of CT(Table 6).

Discussion:

Demography Characteristics of Patients

Most of the patients who comprised the study population were of below 40 yrs. This is in variance to most of the studies of all cause acute pancreatitis which have shown a mean age of 51-64 \pm 15.8-19 yrs $^{11,\ 12}$ in prospective studies, while a retrospective study which evaluated patients with recurrent attacks had a mean age of 43 yrs ¹³. This has also been seen in a series by Raj et al at Kelantan in Malaysia and Kandasami P et al, where peak incidence was seen in the third decade and fourth decade respectively ^{14, 15}. Though, in another retrospective study done by Battersby C and Chapuis P in Queensland, Australia showed 63 % patients were more than 50 yrs¹⁶. According to the gender, 19 patients were males 63.33 % and 11 subjects were females 36.6 %. The ratio of M:F were = 1.9:1.1. This finding is different from a study by Jacob et al in a study group of idiopathic pancreatitis reported an M:F ratio of 2.4:1¹⁷. It was also found that acute pancreatitis was seen in mostly uneducated and family with < 5000 Rs monthly income, muslim and married patients. These results suggest a changing epidemiology of acute pancreatitis in the recent time.

Radiological findings and acute pancreatitis

USG Abdomen:

Among the 30 patients who had undergone repeated USG abdomen examination, 18 of them had no associated findings, 3 of them had suspected biliary sludge where as 6 patients were having fatty liver. In a study done by Gómez NA on USG abdomen findings in а Gastroenterology unit had revealed that 13.2 % had biliary sludge^{18, 19}. One of the recent studies shows that harmonic USG has a higher sensitivity for detection of biliary sludge, while another study²⁰ found a sensitivity of 80 % on endoscopic USG for biliary disorders in "idiopathic pancreatitis", majority of them had sludge present²¹.

CECT :

Contrast enhanced CT scans of abdomen was done for all patients. Initial evaluation revealed varying degree of severity. In CMV, 37.5% subjects were diagnosed to have Grade C severity followed by Grade D 25% and Grade E 25%

Non gallstone and non alcoholic acute pancreatitis respectively. In SOD Grade E 100%, mumps Grade B in 100% , Hepatitis , Choledochal cyst and Tumour Grade E, Pancraes divisum showed Grade C 50 % and Grade B 50 % severity. In fact, the study by Karsenti D et al reports the incidence of Grade D or more pancreatitis in 46 % patients which correlates with the results of the present study ²². One of the patients in this study had evidence of cholelithiasis on CECT abdomen but it was not evident on USG examination, though none of them showed choledocholithiasis.

Fig 1: CT scan of acute necrotizing pancreatitis.

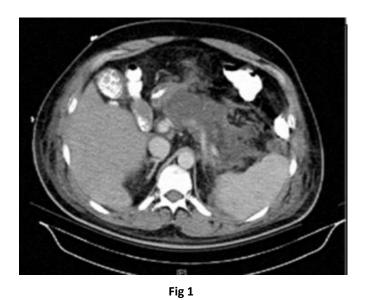


Fig 2 : ERCP showing choledochal cyst near the ampulla causing acute pancreatitis

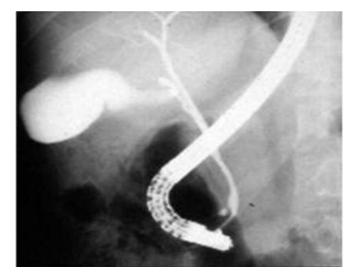


Fig 2



ERCP and MRCP :

ERCP was diagnostic/ assisted in diagnosis in 6 patients on whom this procedure was done. 50 % of the subjects showed stricture of main pancreatic duct in ERCP, delayed excretion in SOD, stricture of main pancreatic duct in EBV, pancreas divisum in all cases of pancreas divisum. ERCP found an underlying cause of pancreatitis in 68 and 32-70 % cases in the "apparently idiopathic" pediatric and adult group respectively, while 52-56 % of pediatric patients studied with recurrent acute or chronic pancreatitis had ERCP , none of them showed cholelithiasis/ choledocholithiasis²³.

Fig 3: ERCP showing pancreas divisum

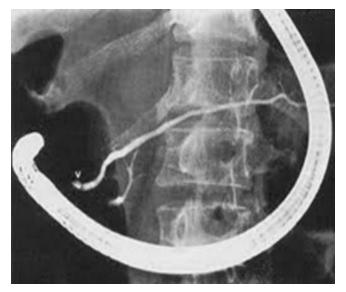


Fig 3

MRCP made a diagnosis/ assisted in diagnosis among 4 patients on whom the study was performed. MRCP revealed 4 structural lesions . MRCP plays a complimentary role in the surgical diagnosis of pancreatic disorders. Testoni PA et al has concluded in his study on idiopathic recurrent pancreatitis MRCP-S-guided approach gave diagnostic accuracy comparable to ERCP with regard to morphologic lesions. It can be used as an alternative, avoiding ERCP-related complications in the diagnostic phase²⁴.

Biochemical and Serological findings and acute pancreatitis

Serum Amylase

The diagnosis of acute pancreatitis was based on the clinical presentation and raised serum amylase along with characteristic USG abdomen findings. In this study serum Amylase was raised > 3 times normal among 80 % subjects. The mean serum amylase level was 627.17 ± 443.5 SU/L with a range of 160 to 2521 SU/L. In a study by Gumaste VV Serum amylase varied from 11 to 416 U/L [mean 58 +/- 46 (SD)]. The maximum elevation noted in this group was 416 U/L. Serum amylase in another group was from 124 to 13,000 U/L (mean 1620 +/- 1976), a level of > 3 times the normal level of amylase reported to have a sensitivity of 72 % and specificity 99 % by Gumaste VV et al ^{25, 26}.In a study reported by Spechler SJ

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et al confirmed that serum amylase was normal among patients with acute pancreatitis ²⁷.

Liver Function Tests :

Liver function tests were done in all patients during the attack looking for abnormalities, which would predict the etiology. Amongst all patients, 18 of them had an abnormal LFT. LFT was normal in 62.5% cases of CMV, whereas LFT was found to be abnormal in SOD, EBV, mumps, hepatitis, choledochal cyst and drugs. Many similar studies and their findings studies have shown LFT abnormalities in the range of $3.5\% - 35\%^{14}$. These results suggest a link between abnormal LFT in patients with non-alcoholic and non-gallstone pancreatitis and possible association but the results of present study are significantly higher.

Sweat Chloride Test :

Among all patient the on whom sweat chloride test was performed revealed normal values. However, recent reports have shown mutation of CFTR gene to be present in "idiopathic" acute pancreatitis, although, there are equally conflicting reports in the recent times $\frac{28,29}{28}$.

Virological Studies :

All patients who were included in the study underwent serological studies for various viral infections. IgM antibody to HIV, HCV, HEV, CMV, EBV, mumps and HBsAg was looked for during the acute episode itself. HBsAg and antibody to HCV and HIV were negative in all patients. Although, there have been many reports to suggest etiological role for HIV infection, hepatitis B and C infections for acute pancreatitis, these have been mostly single cases / or short series³⁰⁻³³.

There were only 2 cases that were HEV positive. In a study conducted by Jain P et al. concluded that acute pancreatitis occurs in 5.65% patients with acute viral hepatitis and recovers with conservative management. Among the various strains of Hepatitis viruses, HEV was the commonest type to cause acute pancreatitis $^{34, 35}$. There were 8 patients having IgM antibody for CMV positive. The remaining patients who underwent tests were all negative for antibodies to CMV, EBV and mumps virus. The serology for CMV being positive among the patients of acute pancreatitis suggests a strong association of this infection with acute pancreatitis and a probable etiological role. CMV infection has also been similarly reported both in immune competent and immune deficient (HIV & post transplant setting) patients. Until mid-1990s in the United States, pancreatitis due to CMV was mainly diagnosed at autopsy in AIDS patients ^{36, 37}.

Miscellaneous findings and Clinical features

In this study 29 patients had presented with classical abdominal pain with radiation to back. (the intended meaning of preceding sentence is not clear) Most of the patients were reported to have prior attacks of acute



pancreatitis < 3 attacks which was found in most of cases. In CMV with acute pancreatitis 75% of the subjects were having < 3 prior attacks, > 3 prior attacks were found in 50% cases of HEV and in all cases of choledochal cyst 100%. Recurrence of attack < 1 during evaluation occurred in most of the cases 90%. Total number of attacks > 3 occurred in all cases of EBV, HEV, gallstone and in 25 % of cases of CMV. Complication of Acute Pancreatitis such as infected necrosis was found in HEV, whereas in CMV there were Pseudocyst in 25% of cases and abscess in 12.5% cases. Follow up of patients were > 12 months in 60% of cases. Follow up > 12 months was conducted in SOD, HBV, mumps, choledochal cyst, pancreas divisum and in 37.5% cases of CMV. Most of the prospective studies in all causes pancreatitis looking at this subject, however have reported lower rates of recurrences varying from 4-11 % ³⁸⁻⁴⁰ which is in variance with the results of the present study. This can possibly be explained by the fact that all above guoted studies had fewer number of patients ranging 20-30 % with alcohol related pancreatitis. But when this issue was considered in the 'apparent idiopathic" group of patients, the results varied by 3.3 % over follow up of mean of 36 months ^{41, 42} as reported by Ballinger et al and Norton et al respectively. This has been discussed in a study by Gullo et al $^{\rm 13}$ in 2002 where 27 % of 1068 patients formed the recurrent acute pancreatitis group and amongst these patients 17 % of the patients belonged to the miscellaneous and idiopathic group, while another study by Coyle et al in 2002 revealed 66 % of patients have recurrent attacks in the "apparently idiopathic" pancreatitis group⁴³.

Conclusion

The etiological factor available in this study was 66.7 % among the patients of non-alcoholic and non-gallstone pancreatitis. Most common etiological factors were CMV followed by HEV. Among the remaining 33.3 % study group patients, no etiological factor was forthcoming, with the help of the diagnostic workup that was used in the present protocol. The achieved results suggest that a rather diligent workup including a biliary microcrystal analysis, a sphincter of Oddi manometry and possible gene analysis for hereditary disorders be relevant to reduce the apparently idiopathic group in the analysis of such patients.

Limitation of the study

This research is a hospital based study from a medical college and hospital of Kolkata, India. A multi centric hospital based study with larger sample size will be practically beneficial to identify the etiological factors of non alcohol and non gall stone acute pancreatitis in India.

Relevance of the study:

The study can provide baseline data for researchers for further investigation.

Author's Contribution:

IB designed the study, collected the data and drafted

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manuscript. IB2 helped in designing the study drafting the manuscript and revision of the manuscript. KND assisted in manuscript write up. IB and BS helped in statistical analysis and interpretation. SK, PB and BR helped in the language and grammar editing. KND, IB, SMB and PB critically revised the manuscript along with IB2. All the authors approved the final document.

List of Abbreviations

- SAARC = The South Asian Association for Regional Cooperation
- CMV= Cytomegalo virus
- HEV = Hepatitis E Virus
- EBV= Epstein Barr Virus
- MRCP= Magnetic resonance cholangiopancreatography
- MRCP-S=Magnetic resonance cholangiopancreato graphy with secretin test
- ERCP = Endoscopic Retrograde Cholangio- Pancreatography
- CECT = Contrast-enhanced computed tomography
- WHO = World Health Organization
- ALP= Alkaline phosphatase
- LFT= Liver Function Test
- SOD= Sphincter of oddi dysfunction
- SVT= Splenic vein thrombosis
- IHBRD= Intrahepatic biliary radicle dilatation

Acknowledgements:

The authors are thankful to authority of Kolkata medical college and hospital for the kind cooperation to conduct the study. The authors are thankful to their families for constant help, support and time.

Conflict of interest:

There is no conflict of interest among authors arising from the study.

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Article Information					
Article history					
Received	16 th October 2013				
Received in revised form	24 th May 2014				
Accepted	26 th June 2014				