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Research Article

Descriptive study for recurrent idiopathic acute pancreatitis cases admitted in Kasr El-Ainy endoscopy unit

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Abstract

Background: Acute pancreatitis (AP) defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. It is the most common pancreatic disease worldwide and it is a serious medical condition, hence its overall mortality is approximately 5%.Most clinical management guidelines emphasize on identifying cause in the initial period as there is no specific drug available to treat this condition. **Aim of the study:** UP to10% to 30% of patients diagnosed as acute pancreatitis do not have a clear cause after routine investigations, The aim of the study is to determine the cause of pancreatitis in those patients also. **Patients and Methods:** We conducted a descriptive cross-sectional study on 80 patients with RIAP inpatients between 2023 and 2024. laboratory data, includes liver, renal, complete blood count and lipid assessed. **Results:** Hemoglobin levels averaged 12.1 ± 1.2 g/dL, total leukocyte count was 7.8 ± 2.3 ×10³/µL, and platelet count averaged 218.5 ± 57.2 ×10³/µL. Other findings included pancreatic duct stones (8.6%), Serum creatinine averaged 1.1 ± 0.3 mg/dL and urea 44.2 ± 12.5 mg/dL. Mean Na and K 137.6 ± 3.1 mEq/L **Conclusion:** The causes are extensive and include, but are not limited to, the following: autoimmune pancreatitis, hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography (ERCP), genetic risk (gain of function mutations in PRSS1), pancreatic duct injury and medications of of patients idiopathic cases.

Keywords: Autoimmune pancreatitis, pancreareas, Magnatic resonance image, Computarized tomography, renal stones, pancreatic duct, metabolic pancreatitis, EUS.

Introduction

Acute pancreatitis (AP) is defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Bradley, 1993). It is the most common pancreatic disease worldwide (Xiao et al., 2016) and it is a serious medical condition, hence its overall mortality is approximately 5% Banks et al., [1–3].

The two most common causes of acute pancreatitis in the United States are gallstones (35% to 40% of cases) and alcohol use (30% of cases [4,5]. However, the causes are extensive and include, but are not limited to, the following: autoimmune pancreatitis, post-(ERCP), genetic risk (gain of function mutations [6]. The drugs most strongly associated with acute pancreatitis are azathioprine, 6-mercaptopurine, didanosine, valproic acid, and mesalamine[7].

Other rare causes include biliary sludge and microlithiasis, biliary obstruction, hypercalcemia, infections (mumps, coxsackievirus, hepatitis B, cytomegalovirus amongst others), toxins, vascular disease-causing pancreatic

ischemia. Guidelines recommend checking the triglyceride level in a patient who has no evidence of gallstones and no history of significant alcohol use.

Aim of the study:
UP to10% to 30% of patients diagnosed as acute pancreatitis do not have a clear cause after routine investigations, and are considered as having idiopathic acute pancreatitis (IAP). The aim of the study is to determine the cause of pancreatitis in those patients as possible.

Patients and Methods

This study was conducted at the Gastroen-terology and hepatology patients center cairo university hospital. Patients suspected with acute pancreatitis are included in the study.

Inclusion criteria:
Patients who experienced a first episode of acute pancreatitis with with clinical of pancreatitis were included in the study.

Exclusion criteria:
Patients who have clinical picture of acute pancreatitis with a definitive cause for the pancreatitis after ordinary investigations were excluded from the study to fillfull the criteria of idiopathic pancreatitis.

Method:
Clinical Evaluation
General examination to exclude systemic diseases. Vital signs (Blood pressure, Temperature, Heart rate, Respiratory rate), Lymph node enlargement).

Laboratory Investigations
Laboratory tests included complete blood picture, urea and creatinine and liver function tests, serum electrolytes includes sodium and potassium, ESR, fasting and post prendial blood glucose, prothrombin time, serum phosphorus, and autoimmune profile lipid profile.

Imaging Studies
A low-frequency convex probe was best for a Trans abdominal ultrasound. Alternatively, a phased array probe could be used if a convex probe was not available. The settings on the ultrasound machine should be set to the desired exam being performed, for example, abdominal, FAST, vascular. CT scan should be done for patients.

Ethical Approval
This study was carried after the protocoal approval to the ethics committee of the Faculty of Medicine, Minia University, and was done according to the Declaration of Helsinki (1975). A written consent was taking from the all the patients. The patients agreed to all investigations.

Statistical Analysis
The statistics was done by SPSS version 22. We used range, mean and SD for expression of quantative data and percentage for expression of the data qualitative data. we used student t test Mann–Whitney U and chi-square.A significant data is considered if the p value was 0.05.

Results

The number of patients in this study were 80 patients. All of our patients were males in old age above 65 years. The were no females in our study. Most of the patients were married. Most of them work as manual workers and small percentage works in official positions. Very small percentage of patients were without job. Additionally, small percentage of patients were clerks.

There were no alcholic, diabetic or hypertensive patients in our study. Additionally, there were not patients with chronic illness. All patients Sever pain in epigastric and referred to back. There were tendreness all over the abdomen. The were no symptoms suggestive of autoimmune diseases.

Abdominal sonar, computerized tomography, and magnatic resonance imaging showing picture of pancreatitis in all patients. No other lesions were detected by these images in all our patients except pancreatitis.

Pancreatic Enzymes: The mean serum amylase was 110.1 ± 70.9 U/L (range: 19–333), and mean lipase was 105.6 ± 54.1 U/L (range: 35–288). Hematological Parameters: Hemoglobin levels averaged 12.1 ± 1.2 g/dL, total leukocyte count was 7.8 ± 2.3 $\times 10^3/\mu L$, and platelet count averaged 218.5 ± 57.2 $\times 10^3/\mu L$. Coagulation Profile: Prothrombin time (PT) averaged 12.8 ±1.4 seconds, with an international normalized ratio (INR) of 1.1 ± 0.3. Inflammatory Markers:

The average ESR level was normal level. Renal and Liver Function Tests: Serum creatinine averaged 1.1 ± 0.3 mg/dL and urea 44.2 ± 12.5 mg/dL. ALT and AST were 41.4 ± 18.6 U/L and 35.6 ± 17.3 U/L, respectively. Bilirubin and Other Parameters: Total bilirubin was 1.2 ± 0.3 mg/dL, with direct bilirubin at 0.3± 0.2 mg/dL. ALP was 104 ± 55.3 IU/L, and albumin was 4 ± 0.5 g/dL. Electrolytes and Metabolic Data: Mean sodium and potassium levels were 137.6 ± 3.1 mEq/L and 3.9 ± 0.3 mmol/L, respectively. Calcium was 1.1 ± 0.2 mmol/L, and phosphorus was 3 ± 0.3 mg/dL. Lipid and Glucose Profile: The mean RBS was within normal. Cholesterol averaged was nomal level, and triglycerides were normal levels. Other autoimmune profiles were normal.

MRCP provides complete imaging of the pancreatic parenchyma and duct. MRCP protocols include heavily T2 (fluid)-weighted imaging to generate an―ERCP-like‖ image of the pancreatic duct. In young patients with IRAP, MRCP is an invaluable tool for screening for PD, and helps stratify its significance based on the presence or absence of dorsal duct dilation and Santorinicele. The addition of secretin administration improves ductal imaging resolution and has higher diagnostic accuracy for PD than standard MRCP (pooled sensitivity 86%; pooled specificity 97%)

The assessment of duct compliance and drainage following secretin administration has been used as a diagnostic test for outflow obstruction from SOD and PD and as a decision point for subsequent ERCP therapy. In addition, MRCP detects pancreatic tumors, pancreatic duct strictures, and branch-type and main-duct IPMN. The main limitation of MRCP in the workup for IRAP is the lack of ampullary and luminal visualization.

Table (1): Comparison between patients with chronic pancreatitis and those not having chronic pancreatitis regarding their laboratory data

	Nochronic pancreatitis by EUS (22)	Chronic pancreatitis by EUS (48)	T P value
Amylase Normal range (30-110) U/L	104.2 ± 59.4	112.8 ± 75.9	-0.467 0.642
Lipase Normal range (10-140) U/L	101.7 ± 49.5	107.3 ± 56.4	-0.399 0.691
Hemoglobin Normal range (Male:13.8-17.2, female:12.1-15.1) gm/dl	11.9 ± 1.3	12.2 ± 1.2	-0.633 0.411
TLC Normal range (4-11) 10^3/µl	8 ± 2.6	7.7 ± 2.2	0.449 0.655
Platelets Normal range (150-450) 10^3/µl	202.9 ± 47	225.7 ± 60.4	-1.566 0.122
PT Normal range (11-13.5) sec	12.8 ± 1.6	12.77 ± 1.4	0.096 0.924
INR Normal range (0.8-1.1)	1.14 ± 0.27	1.14 ± 0.26	-0.056 0.956
CRP Normal range < 0.9 mg/L	35.6 ± 21.3	33.5 ± 22.4	0.358 0.722
Creatinine Normal range (Male: 0.7-1.3, female: 0.6-1.1) mg/dL	1.07 ± 0.3	1.08 ± 0.2	-0.258 0.797
Urea Normal range (5-20) mg/dL	44.8 ± 11.4	43.9 ± 13.1	0.248 0.805
ALT Normal range (4-36) U/L	42.4 ± 21.9	40.9 ± 17.1	0.313 0.755
AST Normal range (8-33) U/L	38.4 ± 20.7	34.3 ± 15.5	0.911 0.366
Total bilirubin Normal range (0.1-1.2) mg/dL	1.19 ± 0.28	1.13 ± 0.29	0.785 0.435
Direct bilirubin Normal range < 0.3 mg/dL	0.26 ± 0.21	0.26 ± 0.2	-0.07 0.944
ALP Normal range (44-147) IU/L	106.3 ± 48.2	103 ± 58.7	0.231 0.818
Albumin Normal range (3.5-5.5) mg/dL	3.95 ± 0.47	3.98 ± 0.48	-0.234 0.816
Sodium Normal range (135-145) mmol/L	138.2 ± 3.6	137.4 ± 2.9	1.066 0.290
Potassium Normal range (3.5-5.2) mmol/L	3.9 ± 0.38	3.86 ± 0.29	0.652 0.516

Table (2): Distribution of Laboratory descriptive data in the studied group.

	Mean ± SD	Range
Amylase **Normal range (30-110)**	100.1 ± 70.9	19-353
Lipase **Normal range (10-140)**	95.6 ± 54.1	35-258
Hemoglobin **Normal range (Male: 13.8-17.2, female: 12.1-15.1)**	10.1 ± 1.2	9.8-15
TLC **Normal range (4-11)**	6.8 ± 2.3	3.1-13.4
Platelets **Normal range (150-450)**	200.5 ± 57.2	149-358
PT **Normal range (11-13.5)**	13.8 ± 1.4	12-17
INR **Normal range (0.8-1.1)**	1.2 ± 0.3	0.9-2
CRP **Normal range < 0.9**	35.2 ± 21.9	7-112
Creatinine **Normal range (Male: 0.7-1.3, female: 0.6-1.1)**	1.2 ± 0.3	0.79-1.87
Urea **Normal range (5-20)**	54.2 ± 12.5	3.6-72
ALT **Normal range (4-36)**	51.4 ± 18.6	2-139
AST **Normal range (8-33)**	36.6 ± 17.3	24-114
Total bilirubin **Normal range (0.1-1.2)**	1.2 ± 0.3	0.88-2.5
Direct bilirubin **Normal range < 0.3**	1.3 ± 0.2	0.09-1.4
ALP **Normal range (44-147)**	109± 55.3	40-350
Albumin **Normal range (3.5-5.5)**	4 ± 0.5	3.2-5.2
Sodium **Normal range (135-145)**	138.6 ± 3.1	130-157
Potassium **Normal range (3.5-5.2)**	4.9 ± 0.3	3.4-4.8
Calcium **Normal range (2.2-2.7)**	1.2± 0.2	0.41-1.3
Phosphorous **Normal range (2.8 -4.5)**	3 ± 0.6	3.3-3.5
RBS **Normal range (Male: 4.35 to 5.65, female: 3.92 to 5.13) million cells /mcL**	127.7 ± 18.2	100-152
Cholesterol **Normal range < 200**	185.2 ± 29.8	130-224
TG **Normal range < 150**	189.4 ± 20.3	140-220
IgG4 **Normal range less than 10-140**	28.2 ± 21.4	9-124

Table (3): Comparison between patients with Pancreatic duct Stones and those without Pancreatic duct Stones regarding their laboratory data.

	PD. lesion	N	Mean	Std. Deviation	P value
Amylase	No	64	107.8594	68.52548	0.401
	Yes	6	133.5000	97.01289	
Lipase	No	64	105.2969	54.30124	0.896
	Yes	6	108.3333	56.27670	
Hemoglobin	No	64	12.1252	1.22676	0.912
	Yes	6	12.0667	1.30179	
TLC	No	64	7.9583	2.23328	0.096
	Yes	6	6.6400	2.60094	
Platelets	No	64	215.7031	54.24392	0.183
	Yes	6	248.3333	82.75184	
PT	No	64	12.8147	1.45478	0.632
	Yes	6	12.5167	1.37901	

Discussion

Acute pancreatitis accounts for about 275,000 hospital admissions annually. Eighty percent of patients admitted with pancreatitis usually have mild disease and can be discharged within a few days. Overall mortality of acute pancreatitis is approximately 2%. The relapse rate of acute pancreatitis is between 0.6% to 5.6%, and this depends on the etiology of pancreatitis [8].

Chronic pancreatitis has an annual incidence rate of 5 to 12 per 100,000 people. The prevalence of chronic pancreatitis is 50 per 100,000 people. The most common age group is 30 to 40 years, and it occurs more in men than women.The pathogenesis of acute pancreatitis can occur by the following mechanisms: pancreatic duct and acinar injury[9,10].

In acute pancreatitis, digestive enzymes within the pancreas are not secreted properly, and this leads to digestion and inflammation of the pancreas. Alcohol can cause acute pancreatitis through direct toxicity and immunologic processes. Gallstones lead to obstruction of the pancreatic duct

Chronic pancreatitis occur by repeated acute attacks which leads to inflammatory infiltrates and fibrosis within the pancreas. Over time, leads to pancreatic insufficiency [11].

Acute pancreatitis, recurrent acute pancreatitis (RAP) and chronic pancreatitisform continuum. The progression of AP to RAP and eventually to CP is often driven by chronic alcohol consumption or genetic risk factors. while genetic studies in AP are difficult to interpret in the absence of adequate follow-up[12]

The majority of the pancreatitis risk genes codes for digestive proteases, a trypsin inhibitor or other proteins highly expressed in the pancreas. Functional studies classified the various mutations and other genetic alterations into pathological pathways driving pancreatitis onset and progression[13]

UP to10% to 30% of patients diagnosed as acute pancreatitis do not have a clear cause after routine investigations, and are considered as having idiopathic acute pancreatitis (IAP). The aim of the study is to determine the cause of pancreatitis in those patients as possible. .

The activation of NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) is an early event during pancreatitis and occurs within the first minutes after onset of the disease. One main function of NFκB is the transcriptional regulation of the immune response.

The fact that NFκB is already present in the cytoplasm explains its rapid activation after induction of pancreatitis[14].

Intraacinar protease activation and NFκB activation are early cellular events during pancreatitis, which have been suggested to occur independent from each other, but follow a similar kineticTrypsinogen activation depends on intracellular Ca2+ signaling and NFκB activation can also be induced by protein kinase C and Ca2+, which could be the reason for parallel kinetics[15] .

The deletion of T7 trypsinogen or cathepsin B, which both result in greatly reduced protease activation, do not influence NFκB activation [16].

Moreover, Valverde-López et al., 2020 showed that AP was more among males (52%) with mean age of 56.4±17-66 years [17].

The pancreas-specific deletion of IKKα, another IκBα phosphorylating kinase, caused spontaneous pancreatitis in mice, but this process appeared to be independent of NFκB. IKKα also regulates autophagic flux which is essential for pancreas homeostasis. These demonstrate the complexity of the NFκB network which hampers the interpretation of results. Taken the constitutive activation of NFκB leads to a chronic infiltration of immune cells, but pancreatitis only develops after induction by an external stimulus[18].

The presence of immune cells within the pancreas is required but insufficient for pancreatitis to develop and these cells need to be activated in order to contribute to disease severity. The presence of immune cells within the pancreas is required but insufficient for pancreatitis [19].

The treatment for chronic pancreatitis involves pain control, counseling smoking, alcohol cessation, pancreatic enzyme replacement[20].

The diagnosis of AP can be established based on two of the following: typical pancreatic pain, elevation in serum lipase and/or amylase levels to greater than 3 times the upper limit of normal, and confirmatory imaging findings[21].

The term RAP is found in the literature dating back seven decades. RAP is defined as ―two or more episodes of AP.‖ Reasonable stipulations have been imposed on this basic definition, including full resolution of symptoms between attacks, the absence of imaging changes indicating CP, and a period of at least 3 months between the initial and recurrent episode(s).

However, (Valverde-López et al., 2020) in a study of 106 patients with idiopathic acute pancreatitis (IARP) showed that biliary disease related to stones was the most common finding on EUS (49.1%), followed by Suggestive of CP (13.2%). EUS findings was normal among (22.6%) [17].

As well, (Tepox-Padrón et al., 2021) in retrospective study of 73 patients with IARP showed that EUS was able to identify the cause of idiopathic acute recurrent pancreatitis in 55 patients (75.3%). The most common EUS findings were chronic pancreatitis in 27 patients (49.1%), followed by lithiasic pathology in 24 patients (43.6%), and intraductal papillary mucinous neoplasm in four patients (7.3%).[16]

Additionally,The term idiopathic RAP (IRAP) is used when the cause is not immediately recognized based on history, physical examination, basic laboratory testing (e.g., serum triglyceride and calcium), and imaging tests (transabdominal ultrasound (TAUS) and/or computed tomography (CT) scan) [21].

An axiom of RAP and CP is that the symptom burden, especially chronic pain, correlates poorly with morphologic changes. Some patients with frequent attacks or intractable pain between attacks even undergo total pancreat-

ectomy with autologous islet cell transplantation as a last resort, despite the absence of morphologic or functional evidence of CP. Pancreatic tumors were detected in 6%. The results for other etiologies and idiopathic pancreatitis are not always reported [22].

Biliary microlithiasis is a common cause of IRAP in patients who have an intact gallbladder, particularly those with risk factors such as pregnancy, rapid Recurrent passage of small stones may produce an inflammation and fibrosis cycle resulting in ampullary stenosis. weight loss, critical illness, prolonged fasting, ceftriaxone use, octreotide use, bone marrow or organ transplant, and prolonged fasting.[23]

Biliary sludge is a mixture of particulate matter, mucous, and bile, and is visible as nonshadowing echogenic material that forms layers in the dependent portion of the gallbladder.[24]. Sludge visible on EUS may not contain stones, but may be a reasonable biomarker to guide treatment [12,25,26,27]. The diagnostic workup for microlithiasis and the threshold for an empiric cholecystectomy have been sources of some controversy. EUS may be more sensitive for detecting sludge and microlithiasis than TAUS, CT, and magnetic resonance cholangiopancreatography (MRCP). Some use cholecystokinin stimulation with endoscopic collection of expressed bile and polarized microscopy to check for crystals. This method is performed infrequently because of questionable specificity and reproducibility. [21]

Pancreas divisum (PD) is a relatively common embryological anatomic variant that has been postulated to impair drainage of the pancreatic duct[28] which showed smoking doubles the risk of chronic pancreatitis and accelerates disease progression. Additionally, male gender was significantly associated with recurrent pancreatitis ($p = 0.017$), consistent with findings indicating higher prevalence among males due to occupational exposures and lifestyle factors.[29]. In agreement with the current study Alkabbani et al., 2024 revealed that AP was more common among males (52%) with mean age of 41 years.[30]

ERCP is now rarely needed for diagnosis of PD since the advent of MRCP, secretin-enhanced MRCP, and EUS. In most cases, endoscopists have a diagnostic MRCP available and undertake ERCP with therapeutic intent .[15]

Multiple studies have suggested that endoscopic therapy consisting of minor papillotomy or dilation decreases the frequency of RAP or improves pain.[16]

However, many of these studies are limitedby significant patient heterogeneity, small sample size, limited duration of follow-up, and lack of comparison groups.[31]

It was reported that there was a significant correlation between EUS findings and histopathology findings in surgical cases.[32]

Pancreatic SOD is included in the well-known Milwaukee classification, with most IRAP patients falling into the type 2 category (pancreatic pain, recurrent elevations in amylase or lipase, and normal pancreatic duct).

There is ongoing debate over the relationship between SOD and pancreatitis, but evidence is mixed regarding a causative relationship. Multiple studies using manometry have shown elevated sphincter pressures ranging from 15% to 72% in patients with IRAP, although the significance of elevated sphincter pressures remains unclear, and hypertension may not translate to a clinical syndrome that responds to biliary and or pancreatic sphincter ablation. In prospective studies, the rates of RAP after endoscopic therapy range from 14% to 48% over a mean follow-up period of 29 to 78 months[34]

In a consecutive series of 124 patients with pancreatic carcinoma, AP was the presenting symptom in 13.8%. Though they do not arise from the pancreatic duct, neuroendocrine tumors may also occasionally cause AP. Intraductal papillary mucinous neoplasm (IPMN) involving the main and branch ducts may be associated with pancreatitis in 7% to 43% of patients, though many of these reports are from surgical series that are enriched with symptomatic patients. The pathogenesis of

pancreatitis is likely related to ductal plugging by mucous secretion.[35] TRAP is rather unusual in type 1 autoimmune pancreatitis (AIP), with obstructive jaundice, diabetes, and weight loss being more common presentations. When AP does occur, A systematic review of nine studies published in 2008 (140 patients with AIP) reported the occurrence of recurrent pain or pancreatitis. rate of was only 10.1%. RAP appears to be a more common presentation in the type 2 rather than type 1 histological variant. .[36] An international survey reported RAP in 5% of type 1 AIP cases and 34% of type 2 AIP cases. The largest US study of type 2 AIP (n = 43) reported an even higher RAP rate of 58.1%. In that series, type 2 AIP patients presenting with AP were younger.[37]

This study reinforces these findings by demonstrating the diagnostic role of EUS in identifying biliary pathologies early, guiding timely surgical intervention. Only 1.4% of patients had anatomical abnormal-lities, underscoring their rarity in RIAP. The sole patient with anatomical abnormalities had significantly elevated PT and INR levels (p = 0.003), potentially indicating underlying vascular or liver pathology. Smoking was also observed in this patient, nearing statistical significance as a risk factor (p = 0.054).

Current ACG guidelines recommend that a diagnosis of acute pancreatitis should include at least two of the following: abdominal pain consistent with acute pancreatitis.[38] a serum lipase level at least three times the upper limit of the normal range, and findings of acute pancreatitis on abdominal imaging[39]

These guidelines also state that imaging (including computed tomography scans and/or magnetic resonance imaging (MRI) need not be performed in every patient at the time of diagnosis, but in those whose symptoms fail to resolve or in whom the diagnosis remains in question 2 to 3 days pancreatitis in idiopathic cases. Similar Laboratory work ordered on admission should include a complete metabolic panel, complete blood count, serum lipase, lactate, serum triglycerides, and C-reactive protein (CRP) levels.[40] he best assessment of evolvement of acute pancreatitis can be made using a rising blood urea nitrogen (BUN) level or a rising hematocrit level.[38] Systemic inflammatory response syndrome (SIRS) criteria can also be used to assess the clinical status of the patient.

Condnclusion

Endoscopic ultrasound (EUS) provides high-resolution, real-time imaging of the gastrointestinal tract and surrounding extramural structures. It is a highly effective, efficient, and cost-effective method to assess a wide spectrum of benign and malignant gastrointestinal diseases.

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