A CASE OF RECURRENT ARRHYTHMIA IN AN ACUTE PANCREATITIS PATIENT – PATHOPHYSIOLOGICAL EXPLANATION USING SHORTAGE OF 'REPOLARIZATION RESERVE'

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SUMMARY – We report a case of a patient with acute pancreatitis who developed serious heart rhythm abnormalities on three occasions, two of which were associated with administration of the first generation antihistamine chloropyramine, and the third one with hypomagnesemia and hypokalemia. Dysrhythmic events consisted of bigeminy, multifocal ventricular extrasystoles and torsades de pointes-like ventricular tachycardia. Electrocardiographic changes in acute pancreatitis in the absence of previous heart disease can occur in more than half of the cases. Antihistamines are medications that are known to produce heart rhythm disturbances, especially the second generation drugs astemizole and terfenadine. This is the first report of chloropyramine causing dysrhythmia. It seems that acute pancreatitis patients are especially prone to heart dysrhythmia caused by different factors such as electrolyte disturbances and pronounced vagal tone. Acute pancreatitis may be added to the list of risk factors with altered 'repolarization reserve', predisposing to drug-induced QT interval prolongation and possible torsades de pointes occurrence.

Key words: *Pancreatitis; Antihistamines; Magnesium deficiency; Hypokalemia; Arrhythmias, cardiac; Torsades de pointes; Long QT syndrome – chemically induced; Case report*

Introduction

It seems that acute pancreatitis patients are especially prone to heart dysrhythmia caused by different factors. We report a case of a patient with acute pancreatitis who developed serious heart rhythm abnormalities in the absence of previous heart disease on three occasions, two of which were associated with antihistamine administration, while the third one was associated with hypomagnesemia and hypokalemia. We discuss the possible mechanisms and review the literature concerning electrocardiographic changes in acute pancreatitis. At the same time, we recognize that acute pancreatitis patients may be a risk group of patients who can develop drug-induced QT interval prolongation.

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Case Report

A 45-year-old man with acute alcoholic pancreatitis was transferred to our University Hospital after

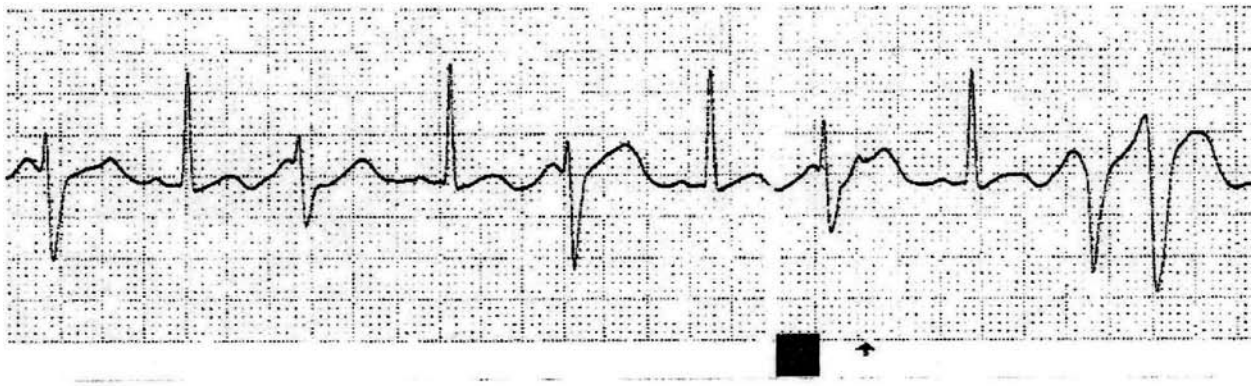
the initial management in a regional hospital due to a severe form of acute pancreatitis. His illness started some 20 days before the transfer and was complicated, apart from peritoneal cavity abscess formation, within acute renal failure necessitating intermittent hemodialysis on several occasions. Medical history from regional hospital indicated that the highest creatinine level was 410 μmol/L, ionized calcium was with the reference levels, hyperglycemia was present (11.4 mmol/L), no data on liver enzymes were available, initial amylase levels were five times above normal; no exact Ranson score was calculated in the beginning of the disease. At our hospital, abdominal computed tomography (CT) scan was done and it showed necrosis of the pancreas, liquid collections surrounding the pancreas, and liquid present in bursa omentalis. Abscess formation was suspected and explorative laparotomy indicated. After laparotomy during which necrectomy and abscessotomy of bursa omentalis and peripancreatic tissue was performed, the patient was admitted to medical-surgical intensive care unit (ICU). Postoperative monitoring, cristalloid and colloid infusion were continued. Through 'feeding' jejunostomy about 24 hours after surgery, enteral nutrition was started along with parenteral nutrition. After the first 24 hours, the patient's APACHE II score was 18. Just one more hemodialysis was performed after the surgery since the patient's renal function improved and he was in the polyuric phase of acute renal insufficiency. His creatinine levels during his ICU stay were below 150 μmol/L with a falling tendency. On day 5, the patient was ordered to receive one unit of packed red cells due to low hematocrit and hemoglobin levels. During transfusion, he developed urticaria-like exanthema accompanied by intense rash. Transfusion was immediately stopped and the patient was given 120 mg of methylprednisolone intravenously (iv.) and the first generation antihistamine chloropyramine 20 mg iv. In the next hour, bigeminy was noted on electrocardiogram (ECG). During this episode of arrhythmia, the patient remained hemodynamically stable and without symptoms. In the next few days, the exanthema persisted and dermatologic consultation was asked for. On day 9, dermatologist prescribed methylprednisolone and chloropyramine. On the same day, within minutes after administration of chloropyramine, the patient developed arrhythmia, bigeminy, and ventricular extrasystoles (VES), which were multifocal, in couplets and with R on T phenomenon (Fig. 1, ECG 1 a,b). The patient experienced nausea, dizziness and chest pain, although remaining hemodynamically stable; arterial pressure was 140/90 mm Hg. During this episode of dysrhythmia, corrected QT intervals according to Bazett's formula were noted and were between 436 and 460 milliseconds. After 80 mg bolus iv. lidocaine, arrhythmia was terminated. It was assumed that arrhythmia was caused by chloropyramine, which was not perceived the first time it had occurred (bigeminy) on day 5 of his ICU stay after the same drug administration. The patient did not receive any other medication that could be arrhythmogenic on either occasion.

On day 14 of hospitalization, the patient experienced another set of arrhythmia with a similar pattern, i.e. multifocal ventricular ectopic beats with R on T phenomenon, and even ventricular tachycardia (torsades de pointes-like) for a brief period of time (Fig. 1, ECG 2). Electrolyte measurement on that occasion showed hypokalemia and hypomagnesemia.

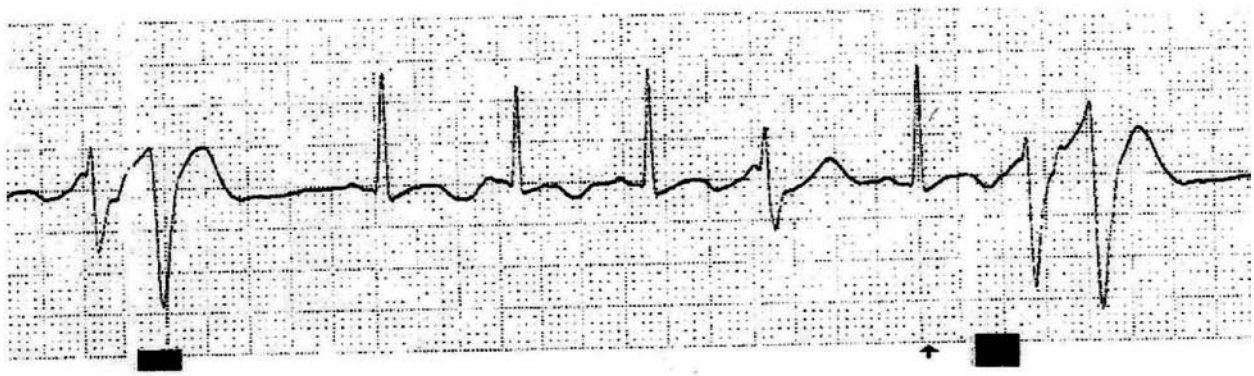
Arrhythmia resolved after bolus lidocaine. Lidocaine was administered in continuous infusion for the next 24 hours. After this event, the patient did not experience arrhythmia any more. During hospitalization in surgical ICU, the patient received potassium and magnesium supplementation on regular basis. On day 21, he was transferred to surgical department in a satisfactory condition.

Discussion

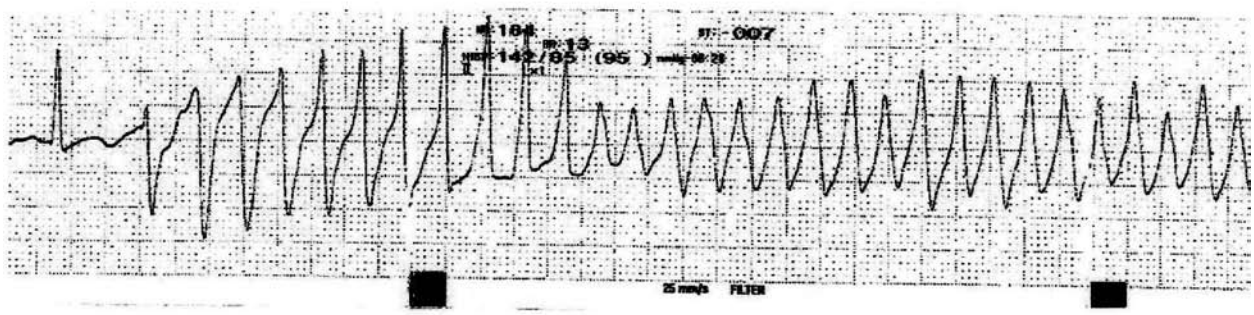
We report a case of a patient with acute pancreatitis with no previous history of heart disease, who developed ECG abnormalities on three occasions during his ICU stay. Electrocardiographic abnormalities are common among patients with acute pancreatitis and are present in more than half of the cases[1-3]. Pezzilli *et al.* studied a group of 56 consecutive acute pancreatitis patients (all without history of heart illness) and found 52.6% of them to have some kind of ECG changes[1]. ECG abnormalities noted were as follows: bradycardia, atrial extrasystoles, changes of the T wave and/or ST segment, disturbances of intraventricular conduction, ventricular ectopic arrhythmia, left anterior hemiblock, complete left bundle branch block, A-V



EKG 1a.



EKG 1b.



EKG 2.

Fig. 1. ECG 1a,b – recorded after the second administration of chloropyramine: pattern of bigeminy and VES couplets with R on T phenomenon; ECG 1a: pattern of bigeminy and couplets of ventricular premature beats with R on T phenomenon; ECG 1b: there are two sets of couplets of VES, with a single VES in the middle. VES appear to be multifocal. ECG 2 – recorded on the third occasion the patient developed arrhythmia. Hypomagnesemia was noted in laboratory results (0.41 mmol^{-1}). Ventricular tachycardia appears to be torsades de pointes-like.

block of first degree, and ventricular fibrillation[1,2]. In the study by Rubio-Tapia *et al*., the most frequent ECG pathological findings were nonspecific changes of repolarization, sinus tachycardia, and left anterior hemiblock[3]. Concerning QT interval variation among patients with pancreatic disease, Ates *et al*. investigated a group of patients with acute biliary pancreatitis and found a significant prolongation of QT interval compared to healthy controls[4]. Belval *et al*. have presented a case of a patient with acute pancreatitis who developed severe bradycardia on several occasions necessitating frequent atropine use[5]. All of these findings could be explained only partially. Electrolyte disturbances are frequent among these patients and can be blamed for the occurrence of ECG pathological findings. Both hypokalemia and hypomagnesemia can result in serious adverse effects on heart automaticity rhythm[6]. Sinus tachycardia can be explained by febrile episode in the course of acute illness or inflammatory complication. In the 1950s, Lieberman *et al*. offered a different kind of solution: they infused trypsin to rabbits, which produced marked changes in the rhythm, and alteration in the P, QRS, S-T and T deflections of the electrocardiogram[7]. Another explanation has been proposed by Hodge and Messer who suggest that vagally mediated 'cardiobiliary reflex' plays an important role. They recorded ECG during biliary surgery and noticed ECG changes when gallbladder and common bile duct were distended[8].

The ECG changes in acute pancreatitis patients and their possible explanation are summarized in Table 1.

Table 1. ECG abnormalities and etiopathogenesis of ECG changes in acute pancreatitis[1-5]

ECG abnormalities in acute pancreatitis
Sinus tachycardia
Bradycardia
Atrial extrasystoles
Atrial fibrillation
A-V block of the first degree
Ventricular ectopic arrhythmia
T wave and/or ST segment changes, nonspecific changes of repolarization
Disturbances of intraventricular conduction
Left anterior hemiblock
Complete left bundle branch block
QT segment prolongation
Ventricular fibrillation
Etiopathogenesis of ECG changes in acute pancreatitis
Electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia)
Cardiobiliary reflex (vagally mediated)
Trypsinemia (experimental model in rabbits)

We analyzed correlation among heart dysrhythmia occurrence, serum electrolyte disturbances, and chloropyramine administration by days in our patient (Table 2).

There were three episodes of arrhythmic events in our acute pancreatitis patient, two of which developed after chloropyramine administration and the third one in the setting of hypomagnesemia and hypokalemia. On the first occasion, the patient was administered chloropyramine, after which he developed bigeminy without symptoms. This had gone unnoticed and it

Table 2. Correlation among heart dysrhythmia occurrence, serum electrolyte disturbances, and chloropyramine administration by days of hospitalization

Day of hospital stay	K (mmol/L)	Mg (mmol/L)	Chloropyramine administration	ECG abnormalities
5	3.4	?	+	Bigeminy
9	3.78	?	+	Bigeminy, multifocal ventricular extrasystoles (VES), couplets of VES with R on T phenomenon QT_c 436-460 milliseconds
14	3.25	0.41	–	Bigeminy, ventricular extrasystole, ventricular tachycardia

was only after the second administration of chloropyramine four days later that we suspected that chloropyramine could be the cause of dysrhythmia. During this episode, the patient developed multifocal VES, with R on T phenomenon, together with the feeling of nausea and chest pain. In fact, antihistamines can prolong QT interval and cause serious dyshrythmia[9,10]. Terfenadine and astemizole, the second generation antihistamines, were especially known for their cardiac toxicity that manifested by the occurrence of torsades de pointes ventricular tachycardia[9]. Concerning antihistamines of the first group, cardiac toxicity is not a class effect and it does not occur through H_1 receptor, although some first generation antihistamines (promethazine, brompheniramine, diphenhydramine) may be associated with prolonged QT interval and cardiac arrhythmia when taken in large doses or overdoses[9]. Our patient did not receive chloropyramine in large doses, in fact, on both occasions arrhythmia occurred after a single dose administration. The corrected QT intervals (QTc) recorded after chloropyramine administration ranged between 436 and 460 milliseconds (ms), which is only slightly prolonged (the reference normal corrected QT is less than 440 ms). Did renal insufficiency add up to the cardiotoxic effect of the administered chloropyramine? We think it is unlikely since the patient's kidney function was normalizing at the time of medication administration. There are numerous groups of medication that can cause QT interval prolongation, such as antipsychotics (the butyrophenones haloperidol, phenothiazines), antiarrhythmics of the first and third group (sotalol), some antidepressants, some antifungals (ketoconazole), macrolides (erythromycin, clarithromycin, azithromycin), antiemetics (ondansetron), and others[10,11]. Many of them are used in the anesthetic and intensive care practice. Our patient was not given any other medication that could have prolonged QT interval except for chloropyramine.

Normal repolarization of heart muscle cells represents a complex interaction among multiple components, namely ion currents such as potassium, sodium and calcium currents that can be outward and inward. The mechanism of acquired, drug-induced QT interval prolongation involves block of the rapid component of the repolarizing outward potassium current[11-13]. This prolongs repolarization, is manifested by prolongation of QT interval on ECG, and causes heart muscle cells to be more susceptible to early after-depolarization[11,13]. QT interval prolongation longer than 500 ms significantly increases the risk of torsades de pointes ventricular tachycardia occurrence[13].

Not every patient exposed to drugs that block potassium current develops exaggerated QT prolongation and arrhythmias and this is one of the reasons why the concept of 'repolarization reserve' was developed by Roden and Abraham[12]. This concept recognizes the complexity of repolarization and involvement of different ion currents in its process (potassium, sodium, calcium ion currents), stressing that potassium outward current is the most important one. As a consequence of this 'reserve', loss of one component of repolarization will not lead to marked QT interval prolongation. Only if repolarization would be challenged by another superimposed event, such as administration of a drug that blocks potassium outward current, QT prolongation will be substantial and could lead to torsades de pointes[12,13]. Interestingly, there is a provocative test using sotalol to assess the stability of myocardial repolarization, developed by Kääb *et al.*[14]. Controlled exposure to sotalol, which blocks repolarizing outward potassium current, successfully identified patients with normal QTc intervals but altered myocardial repolarization and susceptibility to exaggerated QT interval prolongation. Sotalol challenge can be used as a clinical test only in highly controlled environment and in specialized centers[14].

Some of the conditions and risk factors for drug-induced QT interval prolongation and torsades de pointes ventricular tachycardia are female gender, diuretic use, bradycardia, congestive heart failure, hypomagnesemia, hypokalemia, digitalis use, fast iv. infusion of a known QT interval prolonging medication, and others[13]. Acute pancreatitis patients often experience many of these risk factors and conditions in the course of their illness. They can even develop serious heart rhythm disturbances in the absence of other proarrhythmogenic factors. Mofrad *et al.* have described a case of a female patient with acute pancreatitis who developed ventricular fibrillation on several occasions in a setting of prolonged QT interval with no obvious explanation, necessitating insertion of an automatic internal cardioverter defibrillator device[15]. In the same case, cardiac dysrhythmia abated once

pancreatitis had been resolved. It seems that acute pancreatitis patients could possess altered 'repolarization reserve' and might experience serious arrhythmia when challenged by a proarrhythmogenic factor such as electrolyte disturbances or proarrhythmogenic medication administration. We think that acute pancreatitis should be added to the list of risk factors for drug-induced QT interval prolongation and occurrence of torsades de pointes ventricular tachycardia.

On the third occasion, our patient developed malignant ventricular dysrhythmia in a setting of hypomagnesemia (0.41 mmol/L) and hypokalemia (3.25 mmol/L), which first started as bigeminy, then multifocal VES, and finally ventricular tachycardia (torsades de pointes-like). Hypomagnesemia is common in ICU patients, its incidence being as high as 65%[16]. Serum magnesium levels below 0.7 mmol/L are associated with ECG changes indistinguishable from hypokalemia-related effects, including ST segment depression, flattened T waves, and prolongation of PR and QT/QTc intervals[17]. Arrhythmias associated with serum hypomagnesemia include ventricular fibrillation among other possible ECG changes[17]. Hypokalemia alone does not produce serious ventricular cardiac arrhythmias[18]. When combined with other conditions that can promote arrhythmias such as magnesium depletion, digitalis, myocardial ischemia, it enhances the proarrhythmic effects of these other conditions[18]. It is estimated that about 40% of patients who are hypokalemic have associated hypomagnesemia, the leading cause being the use of diuretics[19]. Urinary magnesium losses are most pronounced with the use of loop diuretics such as furosemide. It is important to stress that hypokalemia that accompanies magnesium depletion can be refractory to potassium replacement therapy as long as magnesium deficiency is not corrected[19].

All of arrhythmia episodes in our patient were uneventful owing to prompt diagnosis and immediate therapy. Our case is unique in that it describes serious dysrhythmia in a patient with acute pancreatitis after medication administration. To our knowledge, there are no reports on serious dysrhythmia after chloropyramine administration, which is in use in some countries. Distinct time link between chloropyramine administration and arrhythmia occurrence could be made in our case; on both occasions of chloropyramine administration, arrhythmia developed within minutes. The third occurrence of arrhythmia was due to hypomagnesemia and hypokalemia, but it seems that our patient was especially prone to heart muscle excitability and arrhythmia. Unfortunately, we did not record magnesium levels on the days the patient developed arrhythmia after chloropyramine administration. On the first occasion of dysrhythmia after chloropyramine administration, the patient was hypokalemic (3.4 mmol/L), which must have had an additive effect to arrhythmia occurrence.

There are a few points to emphasize when dealing with acute pancreatitis patients.

- ECG abnormalities in acute pancreatitis are frequent; the etiology is debatable.
- Always beware of hypomagnesemia and hypokalemia as arrhythmogenic factors, be sure to correct them. Remember that many patients who are hypokalemic, also experience hypomagnesemia. Hypokalemia in these cases cannot be corrected unless magnesium supplementation is given.
- In some critically ill patients, several proarrhythmogenic factors can occur at the same time, almost certainly leading to dysrhythmic events.
- When using potentially arrhythmogenic drugs such as antihistamines, antipsychotics, macrolides and other in patients with acute pancreatitis, remember that these patients may already have challenged repolarization and exaggerated QT prolongation. Continuous ECG monitoring during medication administration is essential.
- When dealing with torsades de pointes ventricular tachycardia such as the one in our case, although lidocaine worked, the first therapy option is magnesium sulfate 2 grams iv., irrespective of the serum magnesium levels; potassium should be maintained in the high-normal range (4.5-5.0 mmol/L)[20]. If hemodynamically unstable polymorphic tachycardia or ventricular fibrillation develops, nonsynchronized defibrillation is indicated[20]. One should remember that class IA antiarrhythmics (disopyramide, procainamide, quinidine) and class III antiarrhythmics (dofetilide, ibutilide, sotalol) should not be given to treat these arrhythmias, since they themselves can prolong QT interval and cause tor-

sades de pointes ventricular tachycardia. The data on amiodarone are conflicting, it seems that the risk of torsades de pointes ventricular tachycardia occurrence after its administration is low, although there are some reports that amiodarone can cause torsades de pointes ventricular tachycardia[20,21].

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Sažetak

PONAVLJANE EPIZODE ARITMIJE KOD BOLESNIKA S AKUTNIM PANKREATITISOM – SMANJENJE "REPOLARIZACIJSKE REZERVE" KAO PATOFIZIOLOŠKO OBJAŠNJENJE

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Prikazujemo slučaj bolesnika s akutnim pankreatitisom koji je tijekom liječenja na odjelu intenzivne terapije imao tri epizode aritmije, od kojih su dvije bile povezane s davanjem antihistaminika prve generacije kloropiramina, dok su na nastanak treće epizode aritmije uticale hipokalijemija i hipomagnezemija. Tipovi aritmije kod bolesnika su bile bigeminija, multifokalne ventrikulske ekstrasistole i ventrikulska tahikardija *torsades de pointes*. Promjene u elektrokardiogramu kod bolesnika s akutnim pankreatitisom koji nemaju kroničnu srčanu bolest mogu se javiti u više od polovine bolesnika. Antihistaminici su skupina lijekova koji mogu izazvati disritmije. Ovo naročito važi za antihistaminike druge generacije astemizol i terfenadin. Dosad u literaturi, prema našim saznanjima, nije opisan nijedan slučaj disritmije koja je uzrokovana davanjem kloropiramina. Izgleda da su bolesnici s akutnim pankreatitisom naročito podložni nastanku disritmija uzroci kojih mogu bit elektrolitni poremećaji ili povišen vagusni tonus. Akutni pankreatitis bi se mogao dodati na popis rizičnih čimbenika za nastanak izmijenjene "repolarizacijske rezerve" kardiomiocita, koja može izazvati produljenje QT intervala i ventrikulsku tahikardiju *torsades de pointes*.

Ključne riječi: *Pankreatitis; Antihistaminici; Magnezij, manjak; Hipokalijemija; Aritmije, srčane; Torsades de pointes; Produljeni QT-interval – uzrokovan lijekovima; Prikaz slučaja*