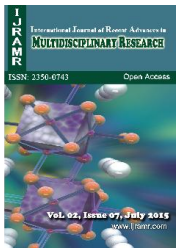

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Research Article

ABNORMALITIES OF SERUM AMYLASE LEVELS IN HIV SEROPOSITVE PATIENTS

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ABSTRACT

OBJECTIVE: We sought to study asymptomatic pancreatic enzyme abnormalities in patients with human immunodeficiency virus (HIV) infection.
METHODS: Serial serum amylase determination was performed in ambulatory HIV-seropositive patients in whom pancreatitis was not suspected.
RESULTS: Eighty-six patients were enrolled in the study. Fifty-two patients (60%) were found to have abnormal amylase values on at least one determination. Only 12 (14% of all patients) had a more than twofold elevation of pancreatic enzymes. Independent factors associated with abnormal pancreatic enzymes were: positive serology for chronic hepatitis B or C, history of intravenous cotrimoxazole administration for the treatment of Pneumocystis carinii pneumonia, stage B of HIV disease, and HIV risk factors other than male homosexuality (mainly intravenous drug use). None of the patients developed clinical pancreatitis.
CONCLUSIONS: Asymptomatic mild to moderate elevations of amylase are common in HIV-positive patients, and are usually associated with positive serology for chronic hepatitis B or C, and medications, especially antiretrovirals and intravenous cotrimoxazole.

INTRODUCTION

Pancreatic lesions, due to opportunistic infections or neoplasms, but more often nonspecific, can be found in 50% of patients with acquired immunodeficiency syndrome (AIDS) at autopsy (1±3). Clinically significant pancreatic involvement is rarely seen antemortem. However, the development of acute pancreatitis has been increasingly recognized in human immunodeficiency virus (HIV)-positive patients in recent years (1± 4). In addition to symptomatic elevations of pancreatic enzymes, there have been reports of unexplained serum amylase elevations, sometimes with concomitant lipase elevations, without clinical evidence of pancreatitis (Murthy *et al*., 1992). Hyperamylasemia in HIV-positive patients can be due to pancreatic pathology, usually pancreatitis, or extrapancreatic causes, such as other gastrointestinal diseases, renal failure, acidemia, macroamylasemia, and pa-rotid glanddisease (Schwartz and Brandt, 1989; Cappell, 1994). We initiated a study aimed at evaluating amylase elevations in HIV-positive patients. Our goal was to determine the frequency of asymptomatic pancreatic enzyme elevations in a cohort of HIV-positive patients in an ambulatory setting and to associate it with potential causative factors.

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MATERIALS AND METHODS

Eligible subjects required documentation of a positive HIV serology and were enrolled as consecutive encounters by the physicians involved in the study in the ART Centre, government General Hospital, Rajiv Gandhi Institute of Medical Sciences, Ongole. Patients, age 18 yr as well as patients with a history of pancreatitis were excluded from the study. History of HIV risk factors, opportunistic infections, medications, and other concomitant illnesses was obtained. All patients were categorized according to the classification system of the Centers for Disease Control (1993 revised) (6). Serum amylase (Manufactured by TRANSASIA BIO-MEDICALS LTD, Nalagarh Road, Village Malpur, Baddl, Dist, Solan in collaboration with ERBA DIAGNOSTICS, Mannhelm/ Germany) concentrations were measured by an automated enzymatic colorimetric assay in the routine chemistry laboratory. The normal range of values for amylase was 25±125 U/L. In addition, CD41 T-lymphocyte counts and biochemical profiles, which included measurements of serum transaminase, globulin, and creatinine concentrations, were performed in most patients. Serological markers for hepatitis B and hepatitis C were available in the majority of patients. Patients positive for hepatitis B surface antigen and hepatitis B core IgG antibodies were considered to have chronic hepatitis B. The categorical variables were compared between groups using the x2 test or the Fisher's exact test and the mean value of

the continuous variables was compared between groups using the t test. Logistic regression analysis was performed using the Statistical Package for Social Sciences for Windows, release 6.1 (SPSS Inc., Chicago, IL). Within a logistic regression model, with backward stepwise selection, variables with a p value # 0.10 were retained. Odds ratios were derived with 95% confidence intervals.

RESULTS

Patients

From February 2014 to January, 2015, 86 consecutive ambulatory HIV-positive patients were enrolled in the study. Of those patients, 58 were men and 28 were women. Their ages ranged between 22±70 yr (mean, 40.8 yr). The mean CD41 T-lymphocyte count was 252cells/mm3. The baseline characteristics of the patients are displayed in Table 1. Seventy-six patients were followed longitudinally for a median duration of 8 months (range, 1±13), with a median number of repeat pancreatic enzyme determinations per patient of four (range, 1±9). For the remaining 10 patients, only baseline determinations were available.

Laboratory Results

All patients had determinations of amylase and atenrollment,. Amylase values ranged from 17± 806 U/L (mean, 117 U/L).
Nine patients were also tested for amylase isoenzymes. At enrollment 31 patients (36%) were found to have pancreatic enzyme abnormalities. Of the patients with ab-normal enzymes at enrollment, 15 patients (17.5% of all patients) had isolated hyperamylasemia, with a mean amylase value of 159 U/L, with either normal or elevated amylase. Twenty-one additional patients were found to have elevated pancreatic enzymes on follow-up determinations. Therefore, at any time data were available (including the 10 patients who were tested once) 52 patients (60%) had enzyme abnormalities detected at least once, and 34 patients (40%) always had normal amylase (Tables 1, 2). Of the patients with enzyme elevations at any time, 26 (30% of all patients) had isolated hyperamylasemia (detected at least once). In the last group, eight patients had isolated hyperlipasemia. Because in half of the patients with elevated enzymes (26/52) a fluctuation of the pancreatic enzymes in and out of the normal range was noted, this method of sequential enzyme determinations was sensitive in detecting abnormalities.

Table 1. Patient Characteristics at Baseline and Comparison Between Groups

Characteristic	Total (N 5 86)	Normal Enzymes (N 5 34)		Abnormal Enzymes (N 5 52)		*p* alue*
Age, yr (mean)	40.8	37		43.4		0.001
Sex, no. (%)						
Male	58 (67)	25	(73)	33	(63)	NS
Female	28 (33)	9	(29)	19	(37)	NS
Risk factor, no. (%)						
IV drug use	36 (42)	12	(35)	24	(46)	NS
Homosexual men	19 (22)	12	(35)	7	(13)	0.017²
Heterosexual	22 (26)	8	(23)	14	(27)	NS
CD41 T-cell count						
.200/mm^3, no. (%)	39 (45)	15	(44)	24	(46)	NS
,200/mm^3, no. (%)	47 (55)	19	(56)	28	(54)	NS
Cells per mm^3, mean	252	334		202		0.04
Stage, no. (%)						
A	19 (22)	12	(35)	7	(13)	NS
B	41 (48)	11	(32)	30	(58)	0.026
C	26 (30)	11	(32)	15	(29)	NS

* For the comparison between patients with normal and abnormal enzymes. The x^2 or Fisher's exact test was used for the categorical variables, and the *t* test for the numerical variables. NS 5 nonsignificant statistically, *i.e.*, *p* . 0.05.
² For homosexuals compared to the other risk factors combined. IV 5 intravenous.

Clinical Evaluations

Seventy five patients (92%) had no gastrointestinal complaints. In seven symptomatic patients (8%) at enrollment, no clinical suspicion of pancreatitis was evident. Of the symptomatic patients five reported epigastric discomfort or dyspepsia, and two reported occasional episodes of nausea or vomiting. Over the course of the study none of the patients developed clinical pancreatitis within a median follow-up period of 8 months. Imaging studies were not routinely performed in the absence of clinical suspicion for pancreatitis. Six patients had either abdominal sonogram or computed tomography (CT) scan performed. Only one patient (who had persistent elevations of both amylase) had abnormalities detected, consisting of mild dilatation of the pancreatic duct and minimal pancreatic enlargement. This patient had a history of alcohol abuse and was also taking antiretroviral drugs (lamivudine and stavudine), which were continued without the development of symptomatic pancreatitis.

An elevation of more than twofold greater than the upper limit of normal for amylase elevation was seen in 12 patients (14% of all patients). Those patients had a more frequent history of Pneumocystis carinii pneumonia (PCP) that was treated either with intravenous pentamidine or intravenous cotrimoxazole (p 5 0.003, x2), and tended to be receiving zidovudine in their antiretroviral regimen (p 5 0.06, Fisher's exact test; data not shown). In two of those patients, amylase isoenzyme determination (performed when isolated hyperamylasemia was present) showed predominance of the pancreatic component. Thus in our study isolated hyperamylasemia was often pancreatic in origin. In three other patients with isolated hyperamylasemia a predominance of the salivary isoenzyme was detected. No cases of macroamylasemia were identified. In another patient a relation-ship to disseminated Mycobacterium avium intracellulare infection with hepatic involvement was possible but not proven by biopsy. Comparing patients with abnormal enzymes as a whole (N 5 52) with the group with normal enzymes (N 5 34), the following factors were

Table 2. Comparison Between Patients With Normal and Abnormal Pancreatic Enzyme(n [%])

Variable	Normal Enzyme (N 5 34)		Abnormal Enzyme (N 5 52)		*p* Value*
Antiretroviral drugs	21	(62)	34	(65)	NS
Cotrimoxazole, *p.o.*	14	(41)	31	(60)	NS
Pentamidine, iv (prior use)	1	(3)	5	(10)	NS
Cotrimoxazole, iv (prior use)	1	(3)	8	(15)	0.064
Pentamidine aerosolized	4	(11)	4	(8)	NS
Chronic hepatitis B²	3	(9)	21	(40)	0.043
Hepatitis C²	0	(0)	6	(11)	0.0015
Pneumocystis carinii pneumonia	2	(6)	10	(19)	0.073
Cytomegalovirus	3	(9)	3	(6)	NS
Mycobacterium avium intracellularae	1	(3)	2	(4)	NS
Systemic candidiasis	3	(9)	2	(4)	NS
Kaposi's sarcoma	4	(11)	0	(0)	0.022
Cryptococcus neoformans	2	(6)	2	(4)	NS
Alcohol abuse (active or past)	10	(29)	9	(17)	NS
Elevated transaminases	17	(50)	31	(60)	NS
Renal failure	4	(12)	3	(6)	NS
Globulins, g/dl (mean)³	3.9		4.4		0.012

* x^2 or Fisher's exact test for the categorical variables, and *t* test for the numerical variables; NS 5 nonsignificant statistically, *i.e.*, *p* . 0.05.
² Based on serology
³N 5 33 for the normal enzyme, and N 5 51 for the abnormal enzyme group. *p.o.* 5 *per os*, iv 5 intravenously.

Table 3. Logistic Regression Model of Abnormal Pancreatic Enzymes

Variable	Adjusted Odds Ratio	(95% Con®dence Intervals)
Chronic hepatitis B or hepatitis C	19.2	(4.0±93.2)
Other HIV risk factors *vs* male homosexuality	9.6	(1.5±61.1)
Stage B *vs* stage A	6.1	(1.07±34.7)
History of intravenous cotrimoxasole administration	24.4	(1.2±511.0)
Age	1.07 (1.0±1.15)	

All significant at *p* # 0.05.

statistically different: age, mean CD41 T-lymphocyte count, stage B of HIV disease, posi-tive serology for chronic hepatitis B, positive serology for hepatitis C, previous history of intravenous cotrimoxazole administration for the treatment of PCP, globulin level, male homosexuality, and Kaposi's sarcoma (see Tables 1, 2). Although significant, the variables positive serology for chronic hepatitis B and Kaposi's sarcoma could not be included in the logistic regression model due to the zero value in one of the cells. However, we included the variable positive serology for chronic hepatitis B or hepatitis C in the model. The factors found to be independently associated with higher risk of abnormal pancreatic enzymes (amylase) were positive serology for chronic hepatitis B or hepatitis C, history of intravenous cotrimoxazole adminis-tration, stage B of HIV disease, and HIV risk factors other than male homosexuality (Table 3). In addition, we identified seven patients in whom a temporal relationship of lipase elevation was evident after 1±3 months of antiretroviral therapy (lamivudine plus either zidovudine or stavudine) initiation. In all cases antiretroviral therapy was continued and lipase values returned to normal.

DISCUSSION

Our results suggest that ambulatory HIV-positive patients can display elevations of pancreatic enzymes without associated evidence for the clinical diagnosis of pancreatitis. We observed mild to moderate usually no more than two times the upper limit of normal asymptomatic elevations of amylase in 36% of HIV-positive patients at enrollment, and in 60% at any time over a median period of follow-up of 8 months. Lambertus *et al*. detected hyperamylasemia in 8% of homosexual men with AIDS-related complex who did not have clinical pancreatitis (Lambertus *et al*., 1990). Pezzilli *et al*. reported a high incidence of asymptomatic elevations of the pancreatic enzymes trypsin and elastase 1 in the serum of 109 HIV-positive patients: 42.2% of patients had elevated trypsin, and 12.8% had elevated elastase, which is comparable to our findings (8). However, determinations of trypsin and elastase are rarely employed in clinical practice. Dowell *et al*. reported pancreatitis (defined by sensitive criteria as elevated serum amylase accompanied by at least one clinical sign or symptom) in 22% of 105 patients with AIDS (Dowell *et al*., 1996), whereas Murthy *et al*. reported pancreatitis (defined as elevated amylase with either a more than twofold amylase elevation, or typical symptoms) in 12 (31%) of 39 AIDS patients retrospectively found to have amylase determinations (Murthy *et al*., 1992). In the latter study, 10 patients with hyperamylasemia underwent autopsy and pancreatitis was demonstrated in two (Murthy *et al*., 1992). Finally, in an intensive care unit setting, 46% (16/35) of AIDS patients were found to have pancreatitis as defined by twofold elevation of pancreatic enzymes (Zazzo *et al*., 1987). Eight of those patients came to autopsy, and all had pancreatic lesions: four nonspecific and four opportunistic infections (Zazzo *et al*., 1987). HIV-positive patients represent a population that may harbor common, as well as unique, pancreatic pathology. A high frequency of medication-associated pancreatitis and a low

frequency of gallstone pancreatitis have been reported in HIV-positive patients (Cappell and Marks, 1995). *Cytomegalovirus* (CMV) infection, as well as other opportunistic microorganisms and neoplasms, can involve the pancreas with or without clinical pancreatitis (1± 4, 12, 13). In addition, HIV has been implicated as a possible cause of pancreatitis in a patient without any identifiable etiology (Cappell, 1994). We found that a history of PCP was associated with a more than twofold elevation of either amylase (five of the 12 patients with PCP received treatment with intravenous pentamidine and seven treatment with intravenous cotrimoxazole). Extrapulmonary *Pneumo-cystis carinii* infection was not documented in any of those cases. The use of medications for the treatment of PCP, such as pentamidine or cotrimoxazole, which are known to be toxic to the pancreas (1, 3, 4, 14 ±17), can explain this finding. This interpretation was supported by the results of logistic regression analysis, demonstrating that a history of intravenous cotrimoxazole administration was an independent risk factor for any degree of pancreatic enzyme abnormality. Many previous reports have implicated intravenous cotrimoxazole as a cause of acute pancreatitis (Bonacini, 1991; Schwartz and Brandt, 1989; Cappell, 1994; Bartels *et al*., 1992; Antonow, 1986). We apparently encountered a more silent pancreatic involvement evident only by asymptomatic amylase elevations.

We reported a strong association between pancreatic enzyme abnormalities and positive serology for chronic hep-atitis B or hepatitis C in this study. However, hyperamylasemia has been previously reported in patients with liver diseases (Piteira Barros *et al*., 1986). Therefore, the association between pancreatic enzyme elevations and hepatitis may not be directly related to HIV pathogenesis. Patients with HIV risk factors other than male homosexuality, the majority of whom were intravenous drug users, were at higher risk of developing pancreatic enzyme abnormalities in our study. It is possible that the increased risk of intravenous drug users for chronic hepatitis B or C, which was strongly associated with pancreatic enzyme abnormalities in our study, was a confounding factor. However, the variable HIV risk factors other than male homosexuality remained an independent risk factor for the development of pancreatic enzyme abnormalities in the logistic regression analysis.

Many studies on antiretroviral drugs have reported elevations of amylase (19 ±21). Furthermore, the association between antiretrovirals, especially didanosine, and acute pancreatitis is well known (Bonacini, 1991; Schwartz and Brandt, 1989; Cappell, 1994; Underwood and Frye, 1993). Kahn *et al*. reported that 30% of patients taking high dose didanosine, 20% of patients taking low dose didanosine, and 6% of patients taking zidovudine had amylase elevations .1.3 times the normal range (Kahn *et al*., 1992). Hammer *et al*. reported an incidence of 1.6% of pancreatic enzyme elevations in HIV-positive patients with no AIDS-defining illness taking either zidovudine alone or zidovudine and zalcitabine, zidovudine and didanosine, or didanosine alone (no differences in dis-tribution between treatment groups) (Hammer *et al*., 1996). Asymptomatic amylase elevations that are rarely associated with the development of clinical pancreatitis have been observed in patients taking didanosine (Maxson *et al*., 1992). Whether the pancreatic enzyme elevations detected in the studies cited above were caused by antiretroviral drugs or were detected incidentally is unclear. Our patients who were taking antiretrovirals had no increased risk of developing pancreatic enzyme abnor-malities greater than that of patients who were not taking antiretrovirals, except for the borderline significant higher percentage of zidovudine use (in combination regimens) in patients with a more than twofold pancreatic enzyme elevation (p 5 0.06). However, the number of patients taking didanosine, for which an association with acute pancreatitis has been well documented, was very small (three patients). In seven cases, a relationship of hyperlipasemia to the use of an antiretroviral drug (all regimens included lamivudine plus either zidovudine or stavudine) was apparent temporally.

Our findings also point to a relationship between pancreatic enzyme elevations and the presence of a low CD41 T-cell count (although this was not an independent factor in the logistic regression analysis) and stage B of HIV disease. Pezzilli *et al*. similarly noted a relationship of abnormal pancreatic enzymes with low CD41 cell counts (Pezzilli *et al*., 1992). Dowell *et al*. found that pancreatitis was more likely to occur in patients with AIDS than AIDS-related complex (Dowell *et al*., 1996). It is possible that pancreatic involvement by HIV plays a role in the development of pancreatic enzyme abnormalities. However, patients with advanced HIV disease are more likely to be exposed to medications with potential pancreatic toxicity or to have a history of infections that may involve the pancreas, which can be confounding factors. Finally, as age increases there was borderline increased risk of demonstrating abnormal amylase values. In conclusion, HIV-positive patients coinfected with hep-atitis B or C, or treated with agents associated with known pancreatic toxicity (such as intravenous cotrimoxazole and antiretrovirals), may display asymptomatic pancreatic enzyme elevations, usually less than twofold. Further prospective studies will be required to determine the relationship, if any, of asymptomatic pancreatic enzyme abnormalities to the ultimate course and complication profile of HIV infection.

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