Characterization of chronic calcific pancreatitis in the presence of HIV infection: Comparison with uninfected patients

M Brand
Pretoria pancreatic diseases research group, University of Pretoria, Pretoria, South Africa

Introduction

Chronic calcific pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas. In its later stages it is characterized by both exocrine dysfunction presenting as malabsorption and steatorrhea, and endocrine dysfunction in the form of diabetes mellitus. Alcohol is the most common risk factor.[1] Other factors include smoking, a genetic predisposition and xenobiotic exposure.[2]

There are several causes of malabsorption and steatorrhea in HIV-infected patients including enteric infection, notably by giardia. Human immunodeficiency virus (HIV) infection has been associated with pancreatic exocrine dysfunction.[3,4] The pancreatic mechanism of exocrine dysfunction has not been well elucidated in the literature. Publication of CP in HIV patients is limited to isolated case reports.

Patients with HIV/AIDS are predisposed to a variety of pancreatic disorders, most commonly opportunistic infections, anti-retroviral drug toxicity and neoplasms. Patients with HIV infection are also prone to common risk factors for pancreatic pathology, perhaps even more so because of other pathologies. However most pancreatic involvement in HIV infected patients is silent, and may be overshadowed by other HIV associated symptoms and signs.[5] Pancreatitis in HIV infected patients is mostly acute due to infections and antiretroviral drug toxicity. To date no study has investigated CP in HIV infected patients.

Hypothesis: Given the clear specific and nonspecific risk factors for pancreatic pathology we hypothesized that chronic pancreatitis would be evident in HIV infected patients, and that the illness would be more severe in HIV infected patients.

The aim of the study was to document the occurrence of CP in HIV infected patients, and to compare the profile of the patients, risk factors and the disease manifestation to HIV-infected patients.

Methods

Prospectively collected clinical databases of the Steve Biko Academic Hospital was reviewed for patients diagnosed with chronic pancreatitis with a minimum follow-up period of one year. Chronic pancreatitis diagnosis was based on radiological imaging demonstrating pathognomic pancreatic calcification. Patient information was collected through a research nurse-administered questionnaire on pancreatic disease. This included demographic information, smoking and alcohol use, employment history, psychosocial circumstances, exposure to commonly occurring xenobiotics and clinical information. Following appropriate counselling all patients underwent HIV testing with a HIV enzyme linked immunosorbent assay and if positive a confirmation test was performed. Newly HIV diagnosed patients were placed on ARV treatment. A history of steatorrhea (the patient described loose stools that were difficult to flush away or floated on the surface of the toilet water) or post prandial abdominal bloating relieved by the use of pancrealipase was extracted from the database. Endocrine dysfunction was diagnosed if the HbA1c was greater than or equal to 6.5% at any time. Patients were followed up at the clinic every 3 months for the development of relevant manifestations of CP.

This study was approved by the University of Pretoria Research Ethics Committee (201/2017).

Statistical analysis

HIV infected and -uninfected patients were grouped. The groups were compared with regard to demographics, risk factors and clinical CP history. Descriptive data is represented as means and their ranges. A Student T test was performed for normally distributed continuous variables and a Mann Whitney U test was performed to assess significance of non-uniform continuous variables. A Fisher Exact test was applied to binary values. A p-value of $< 0,05$ was considered significant.

Results

Seventy six patients were identified in the databases with CP. However 12 were either lost to follow-up or diagnosed within 12 months preceding this study and hence excluded. This report analyses the remaining 64 patients with CP. Of these 22 (34%) were HIV positive

Correspondence
M Brand
email: martin.brand@up.ac.za

and 42 (66%) HIV negative. Their demographic and socio-economic data are compared in Table 1.

Table 1: Characteristics of Chronic Pancreatitis Patients

	Whole group	HIV positive	HIV negative	HIV positive vs HIV negative
	N= 64	N =22	N =42	p-value
Age years (Range)	48.9(30-69)	45(31-64)	50.7(30-69)	0.008
Age<45 years old	22	13	9	0.038
Male:Female	54:10	19:3	34:8	0.494
Body Mass Index (kg/m2)	19.0 (14.8-24.5)	18.9 (16.4-22.7)	19.1 (14.8-24.5)	0.77
CD4 count (cells/mm3) (Median(Range))		463 (110-988)	-	-
Antiretroviral therapy		13	-	-
Social History Education (completed standard 8/ Grade 10)	33	12	21	0.231
Currently employed	17	5	12	0.60
Currently married/ life partner	27	7	20	0.887
ECOG score	2(1-3)	2(1-3)	2(1-3)	0.229

HIV infected patients were younger than uninfected patients (p = 0.008), being more likely to be less than 45 years old (p = 0.038). Forty two of the patients were men (84%) but the proportion of males and females did not differ between the groups. The mean BMI of the 2 groups did not differ. More than half the patients had grade 10 education (p = n.s.) but only 13 (26%) were employed (p = n.s.). The CD4 count of the HIV infected patients were not low, despite several of them not being on ARV drugs.

The CP risk factors are compared between the groups in Table 2.

Table 2: Risk Factors

	Whole group	HIV positive	HIV negative	HIV positive vs HIV negative
	N= 64	N =22	N =42	p-value
Ever smoker	56	17	39	0.284
Pack years [Median(Range)]	14 (5-27.5)	12.5 (5-25)	15 (5-27.5)	0.079
Alcohol use	61	21	40	0.46
Petrochemical exposure	32	10	22	0.51

None of the risk factors differed statistically between the groups, although HIV infected patients tended to be heavier smokers (p = 0.079).

The clinical aspects of CP are depicted in Table 3.

Table 3: Chronic pancreatitis history

	Whole group	HIV positive	HIV negative	HIV positive vs HIV negative
	N= 64	N =22	N =42	p-value
Years with CP [Median(Range)]	1(1-23)	1(1-23)	2(1-18)	0.363
Exocrine dysfunction	42	14	28	0.785
Units Creon per meal [Median(Range)]	25000 (25000-75000)	40000 (25000-75000)	25000 (25000-50000)	0.019
Endocrine dysfunction	26	4	22	0.033
Insulin use	17	2	15	0.014
HbA1c	6.8 (3.5-12.3)	5.6 (4.5-8.5)	7.21 (3.5-12.3)	0.025
Albumin [Mean(Range)]	36(14-46)	34(14-43)	37(18-46)	0.053

HIV infected patients had a longer CP history. The effect of CP on the patients' wellbeing did not differ, the groups having similar ECOG scores. The HIV infected patients required more oral pancreas enzyme replacement to control steatorrhea although the proportion with exocrine function did not differ. Significantly more HIV uninfected patients were diabetic (p = 0.033) and required insulin (p = 0.014).

Discussion

The epidemiology of CP has not been as well defined as other pancreatic diseases. Some population based studies have been reported and these are mostly from developed countries. Incidences differ from 4 cases per 100 000 in the UK6 to 13.4 per 100 000 in Finland.[7] A study from the United States of America reported an age and sex adjusted incidence of 4.5 cases per 100 000 person years.[1] The incidence of CP in Japan has been reported as 11.9 per 100 0008 and 4.2 per 100 000 per year for early CP.[9]

No epidemiological studies on CP in Africa have been reported and specifically none from Sub-Saharan Africa which has the greatest incidence of HIV infection in the world. The incidence of CP in patients with HIV infection is not known. A single case report of CP in an HIV patient has been published.[10] An MRI/MRCP study has been published describing only radiological findings of the pancreas in 31 patients with HIV. Sixteen had ductal dilatation but none demonstrated pancreatic calcifications.[11] A pre-HAART era autopsy study of 749 HIV infected patients documented a pathology in 33.9% of pancreas. These were mostly opportunistic infections.[12] No cases of CP were seen. Another autopsy study of 109 AIDS patients, also revealed no cases with features of CP.[13] In the HAART era similar autopsy findings have been reported.[14] CP seems to be rare in HIV infected patients.

South Africa has the highest incidence of HIV infection in the world. Nineteen percent of adults between 15 and 49 years of age (7.52 million people) are infected15 , hence it is to be expected that CP would occur in the HIV population.

In this study of patients with CP, one third of the study population were found to be HIV infected. The study compared the manifestations of CP in HIV-infected and -uninfected patients. The traditional chronic pancreatitis risk factors did not differ between the groups, of the factors interrogated , alcohol and tobacco use were prominent in both groups.

The HIV infected group patients were significantly younger than the HIV uninfected group. The reason for this difference is not discernable from this study. It may be an epiphenomenon in that HIV infection occurs in younger people. It may also be that the progression of pancreatic disease from subclinical to the clinically symptomatic phase is more rapid in HIV infected patients. Subtle and subclinical microscopic exocrine and endocrine pathology occurs in the pancreas of HIV-infected patients16 even in the HAART era.[14] It may be that the development of CP is accelerated in HIV infected patients.

The lower incidence of diabetes mellitus (DM) in the HIV infected patients is unexpected. Both a high prevalence of DM and a low prevalence have been reported in HIV infected patients.[17,18] These population-based studies did not interrogate CP in the subjects. The prevalence found was most likely that of type 2 DM, as opposed to type 3c DM which occurs in CP patients. The HIV infected and uninfected patients

in the present study had the same duration of CP. The incidence of diabetes mellitus would therefore be expected to be the same in the two groups. A hypothesis may be that HIV initially affects acinar cells. With progression of CP disease islet cells may be affected later in the disease course and thus DM may develop later. Additionally, an increase in the number of pancreatic islets has been shown in HIV infected patients.[14] Further research is required to clarify this finding.

Pancreatic insufficiency is underdiagnosed in patients on HIV therapy as many patients in whom a pathogenic infection has been excluded are thought to be suffering from anti-retroviral treatment side effects or have HIV induced small bowel mucosal abnormalities.[19]

HIV infection is associated with a malabsorption syndrome that includes steatorrhea,[20] postulated to occur as a result of multiple factors including intestinal mucosal damage and exocrine pancreatic dysfunction.[4] Studies have shown that HIV with steatorrhea-like symptoms have decreased fecal elastase, however the levels do not determine fat malabsorption as high fecal fat excretion in this study occurred independent of fecal elastase levels.[3] Following the introduction of HAART the incidence of steatorrhea as a result of intestinal mucosal damage decreased significantly, resulting in pancreatic insufficiency becoming the dominant cause of steatorrhea.[21]

Limitations of this study

We do not routinely determine fecal elastase. The patients in this study had severe exocrine insufficiency and not early onset CP. Our diagnosis of CP was based on radiological imaging demonstrating pathognomic pancreatic calcification of chronic calcific pancreatitis. In an HIV positive patient pancreatic calcifications rarely may represent extra-pulmonary infection by pneumocystis jiroveci. However, calcifications in these cases are fine and are often associated with lymph node calcification22 unlike the coarse calcifications seen in CP.

Conclusion

We have described a group of HIV-infected patients with CP. In comparison with a group of HIV-uninfected patients with CP they had the same risk factors but were significantly younger. HIV infection may be a risk factor for the earlier onset of CP in the presence of known risk factors. Chronic pancreatitis should be considered in the differential diagnosis of persistent non-infective diarrhea, or steatorrhea. Significantly fewer HIV-infected patients with CP had diabetes mellitus, despite having the same duration of CP. There may be a pathological disjunction of islet cell pathology between HIV-infected and –uninfected patients.

References

1. *Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol 2011; 106(12): 2192-2199.*
2. *Jeppe CY, Smith MD. Transversal descriptive study of xenobiotic exposures in patients with chronic pancreatitis and pancreatic cancer. JOP 2008; 9(2): 235-239.*
3. *Carroccio A, Di Prima L, Di Grigoli C, Soresi M, Farinella E, Di Martino D, et al. Exocrine pancreatic function and fat malabsorption in human immunodeficiency virus-infected patients. Scand J Gastroenterol 1999; 34(7): 729-734.*
4. *Carroccio A, Guarino A, Zuin G, Verghi F, Berni Canani R, Fontana M, et al. Efficacy of oral pancreatic enzyme therapy for the treatment of fat malabsorption in HIV-infected patients. Aliment Pharmacol Ther 2001; 15(10): 1619-1625.*
5. *Schwartz MS, Brandt LJ. The spectrum of pancreatic disorders in patients with the acquired immune deficiency syndrome. Am J Gastroenterol 1989; 84(5): 459-462.*
6. *Johnson CD, Hosking S. National statistics for diet, alcohol consumption, and chronic pancreatitis in England and Wales, 1960-88. Gut 1991; 32(11): 1401–1405.*
7. *Jaakkola M, Nordback I. Pancreatitis in Finland between 1970 and 1989. Gut 1993; 34(9): 1255-1260.*
8. *Hirota M, Shimosegawa T, Masamune A, Kikuta K, Kume K, Hamada S, et al. The sixth nationwide epidemiological survey of chronic pancreatitis in Japan. Pancreatology 2012; 12(2): 79-84.*
9. *Masamune A, Kikuta K, Nabeshima T, Nakano E, Hirota M, Kanno A, et al. Nationwide epidemiological survey of early chronic pancreatitis in Japan. J Gastroenterol 2017; 52(8): 992-1000.*
10. *Valicenti P, Tomassi L, Acevedo L. Calcified chronic pancreatitis in an HIV positive patient. Medicina (B Aires) 2005; 65(3): 255.*
11. *Bilgin M, Balci NC, Erdogan A, Momtahen AJ, Alkaade S, Rau WS. Hepatobiliary and pancreatic MRI and MRCP findings in patients with HIV infection. AJR Am J Roentgenol 2008; 191(1): 228-232.*
12. *Brivet FG, Naveau SH, Lemaigre GF, Dormont J. Pancreatic lesions in HIV-infected patients. Baillieres Clin Endocrinol Metab 1994; 8(4): 859-877.*
13. *Chehter EZ, Longo MA, Laudanna AA, Duarte MI. Involvement of the pancreas in AIDS: a prospective study of 109 post-mortems. AIDS 2000; 14(13): 1879-1886.*
14. *Barbosa AG, Chehter EZ, Bacci MR, Mader AA, Fonseca F. AIDS and the pancreas in the HAART era: a cross sectional study. Int Arch Med 2013; 6(1):28.*
15. *STATS SA. Mid-year population estimates 2018. [Internet] Statistical release P0302. Statistics South Africa. [cited 2019 March 13]. Available from: https://www.statssa. gov.za/publications/P0302/P03022018.pdf*
16. *Chehter EZ. HIV and Pancreas: What do we know till now? J Pancreas 2018; 19(2): 107-108.*
17. *Abebe SM, Getachew A, Fasika S, Bayisa M, Demisse AG, Mesfin N. Diabetes mellitus among HIV-infected individuals in follow-up care at University of Gondar Hospital, Northwest Ethiopia. BMJ Open 2016; 6:e011175.*
18. *Kavishe B, Biraro S, Baisley K, Vanobberghen F, Kapiga S, Munderi P, et al. High prevalence of hypertension and of risk factors for non-communicable diseases (NCDs): a population based cross-sectional survey of NCDS and HIV infection in Northwestern Tanzania and Southern Uganda. BMC Med 2015; 13: 126.*
19. *Price DA, Schmid ML, Ong EL, Adjukeiwicz KM, Peaston B, Snow MH. Pancreatic exocrine insufficiency in HIV-positive patients. HIV Med 2005; 6(1): 33-36.*
20. *Poles MA, Fuerst M, McGowan I, Elliott J, Rezaei A, Mark D, et al. HIV-related diarrhea is multifactorial and fat malabsorption is commonly present, independent of HAART. Am J Gastroenterol 2001; 96(6): 1831-1837.*
21. *Canani RB, Spagnuolo MI, Cirillo P, Guarino A. Ritonavir combination therapy restores intestinal function in children with advanced HIV disease. J Acquir Immune Defic Syndr 1999; 21(4): 307-312.*
22. *Miller FH, Gore RM, Nemcek AA Jr, Fitzgerald SW. Pancreaticobiliary manifestations of AIDS. AJR Am J Roentgenol 1996; 166(6): 1269-1274.*