Pancreatitis Developing in the Context of Acute Hepatitis: A Literature Review
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ABSTRACT
Despite strong evidence suggestive of associations between hepatic diseases and pancreas injury, a potential relationship between acute hepatitis and acute pancreatitis has not been a matter of review; which we focused on in the current paper. Some of the main findings of this review article are: fulminant hepatitis failure represents the highest incident rate of hepatitis-related acute pancreatitis; so a screening program might be indicative in these patients. Specific characteristics of HAV-related pancreatitis are that it is a benign condition with no reported mortality; and a male preponderance in the incidence, with females developing in older ages and having shown the signs of both conditions simultaneously. The incidence of acute pancreatitis in HBV infection is the lowest, but the mortality was the highest. HEV-related acute pancreatitis was most likely to represent pseudocysts and there was an apparent ethnic-priority with Indian descents, the only program might be indicative in these patients. Specific characteristics of HAV-related pancreatitis are that it is a benign condition with no reported mortality; and a male preponderance in the incidence, with females developing in older ages and having shown the signs of both conditions simultaneously. The incidence of acute pancreatitis in HBV infection is the lowest, but the mortality was the highest. HEV-related acute pancreatitis was most likely to represent pseudocysts and there was an apparent ethnic-priority with Indian descents, the only reported cases in the literature. Hepatitis-related pancreatitis in liver transplant recipients was most frequent in HBV infected patients; and in IFN-induced pancreatitis, cessation of the drug was most effective in treatment, with no catastrophic event reported.

INTRODUCTION
Inflammatory hepatic disease incites infiltration of B and T lymphocytes, dendritic cells and inflammatory cytokines into lymphoid follicles [1-4], and it has been demonstrated that one of the important causes of pancreatitis is autoimmunity [5]. Acute pancreatitis (AP) is not a rare observation in fulminant hepatic failure (FHF) and has been confirmed clinically as well as in autopsy analyses based on histological or serological studies [6]. On the other hand, viral infections, including mumps virus, Coxsackie B virus, Epstein-Barr virus and measles virus, have also been implicated as an etiological factor of AP [7]. Although hepatitis viruses typically have a strong tendency to infect hepatocytes, their antigens have also been detected in tissues of other organs including the pancreas [8]. It has also been reported with hepatitis A (HAV), hepatitis B (HBV), hepatitis non-A non-B or hepatitis C (HCV) and hepatitis E (HEV) virus infections.

Although pancreatitis episodes erupting due to different liver diseases have been largely reported in the literature; nonetheless, its implications are reportedly different when happening due to different etiologies. Even, there is large discrepancy when comparing pancreatitis courses and prognosis within similar backgrounds. In this review article we aim to systematically review the existing literature on any evidence of relation between an acute hepatitis and development of pancreatitis. For this purpose, we categorized our paper into subsections which discuss any potential relationships between pancreatitis developing in the context of different etiologies of acute hepatitis.

LITERATURE REVIEW
An extensive search for articles was performed concerning associations between acute hepatitis of any reason and AP using multiple sources including PubMed, publishers’ websites and the Google Scholar. All articles were assessed for levels of evidence and included to the review article accordingly. The following keyword or combinations of them have been used: acute hepatitis; hepatitis A virus; hepatitis B virus; non-A non-B hepatitis; hepatitis C virus; hepatitis E virus; fulminant hepatic failure; autoimmune hepatitis; transplant patients; drug-induced; interferon; ribavirin; HAV; HBV; HCV; HEV; IFN; RBV; pancreatitis; AP; etc. When the search was done in PubMed, titles proposed by PubMed as related articles were also screened to find more evidence. In the case of Google Scholar, citations of the found papers were screened to find more related reports. Also, references to the found reports were also searched for more related evidences. Only found papers reported either in English or Persian languages were included. Evidence for any of the subtypes of hepatitis and their relations to AP were reviewed in separate subtitles. Finally in the discussion section, a conclusion for each of the reviewed subtitles was prepared from their particular features.
FULMINANT HEPATIC FAILURE

The association of AP with fulminant hepatic failure (FHF) was first identified by Parbhoo et al. in 1973 [9] in 44% of their FHF population with no association to the cause of liver disease. Since that time, some studies have investigated the association and clinical profile of patients with AP and FHF. Recognition of the distinctive features and associations of pancreatitis when developing in combination with FHF will provide us more powerful instruments for clinical management. So, here we review the existing data in the literature on this subject. The frequency of pancreatitis developing in the context of FHF has been reported in different studies, which more or less is about one third of all cases. In the A retrospective study of 30 FHF patients (liver failure reason: 9 drug-induced; 8 HBV infection; 2 Budd-Chiari Synd.; 11 cryptogenic) with imaging methods by Kuo et al. [10] showed that 10 cases developed pancreatitis (diagnosis confirmed by radiological studies), comprising to 33% of patients, while this rate in patients with decompensated chronic liver disease was 7 out of 30 or 23%. Although authors reported a minimal association between the type of liver disease and development of acute pancreatitis, no p value or other data had been presented [10]. A similar study by Ede et al. [11] on 35 FHF patients (paracetamol overdose (27 cases), non-A non-B hepatitis (4), hepatitis B (3) and hepatitis A (one)) also found evidence of AP determined by a distinct raise in serum P3 isoenzyme of amylase in 14 (40%) of patients, indicative of AP 57% of the patients died of the disease course of which included 14 (52%) of patients with paracetamol overdose and 6 (75%) of patients with viral hepatitis. There is also a case report of acute pancreatitis after FHF (diagnosed by clinical manifestations and raised liver function tests) induced by toxic mushroom (Lepiota subincarnata J.E. Lange) toxicity which necessitated a liver transplantation, and finally patients survived [12]. Overall, AP due to FHF seems to have a high incidence; but due to the high mortality rate associated with this condition [13], no judgment can be made on the fatality of AP in FHF patients.

HEPATITIS A VIRUS

To our knowledge, except for one study, all the data from existence of any association between acute hepatitis A virus (HAV) infection and AP comes from case reports and one case series, and only one epidemiological data exists in the literature on the frequency of pancreatitis developing in HAV infection. Jain et al. [14] prospectively followed 16 patients with confirmed diagnosis of HAV infection, and finally 2 (12.5%) of them developed pancreatitis within the 4 weeks after jaundice. Mishra et al. [15] report 5 cases of hepatitis A virus infection (1 female, 4 males; age range: 4-20 years) getting complicated with AP. Abdominal pain, as the first symptom of pancreatitis developed after 10-22 days from the onset of icterus, except in one case whose icterus & rise in serum transaminases presented with pain, simultaneously. All their patients recovered from both hepatitis and pancreatitis with no mortality reported. There are also some case reports indicating such a relationship. Lopez Morante et al. [16] reported a 12-year-old boy with an 8 day delay between start of icterus and abdominal pain. He completely recovered from the condition. Garty et al. [17] report a 4-year-old boy who develops severe abdominal pain after 2 weeks of initiation of symptoms of hepatitis A virus infection. Medical management also brought him full recovery after 5 days. Sudhir Kumar Rana et al. [18] report a 10-year-old boy who developed abdominal pain after 6 days of the onset of hepatitis A infection symptoms. He well responded to conservative management within 7 days of treatment initiation. Shrier et al. [19] report from a 4 year old Korean girl who presented simultaneously with icterus and abdominal pain. Medical management improved her illnesses thoroughly. Basaranoglu et al. [20] report from a 20-year-old woman presenting with icterus and abdominal pain. She recovered from both conditions after 5 days of conservative management. El-Sayed et al. [21] report an 11-year-old girl who developed signs and symptoms of pancreatitis 1 week after icterus. Conservative management brought her full recovery. Moleta et al. [22] report a 26-year-old woman who simultaneously developed signs and symptoms of icterus and epigastric pain. She improved after 6 days of conservative therapy. Despite the scarcity of large clinical studies, the existing data is suggestive of a benign course of AP in HAV patients. Future studies are recommended to confirm our conclusion.

HEPATITIS B VIRUS

Acute hepatitis B virus (HBV) infection has also been reported to be associated with development of AP. In their prospective study, Jain et al. [14] followed 54 patients with confirmed diagnosis of acute hepatitis B virus infection for at least 4 weeks, and finally detected 1 (2%) of them developing signs of AP, detected by imaging procedures. The lower percentage of patients diagnosed with AP in patients with acute hepatitis B virus infection compared to infection by other hepatitis viruses almost reflects the number of reports in the literature; with the least number of reports for such a relation for HBV infection. Yuen et al. [23] report a series of five patients (4 males, 1 female) with acute exacerbation of chronic HBV infection that simultaneously developed AP, and compared their data to 85 cases of AP due to other etiologies and 406 patients with an acute HBV exacerbation episode. Finally 4 (80%) of the patients in the case (HBV) group died of pancreatitis, while in the controls with pancreatitis, the mortality rate was 13 (15%), and in those with only acute HBV exacerbation, only 9 (2.2%). A report from a 63-year-old man who underwent combined hepatitis A and B vaccination indicates developing acute necrotizing pancreatitis following vaccination, though the patient got thoroughly recovered [24]. In a 32-year-old male liver transplant recipient in whom serum profile had been performed, the rise in serum amylase levels indicative of an AP episode was almost overlapping the HBV DNA profile [25]. HBV markers have also been found in chronic
alcoholic pancreatitis [26]. An interesting case of chronic HBV infection has been reported by Chen et al. [27] in whom the patient represented by repetitive episodes of AP which would have been controlled with lamivudine therapy, and while the patient was on lamivudine, he would have remained in remission. Nonetheless, shortly after cessation of lamivudine, pancreatitis episodes would return that shows the effects of lamivudine therapy in control of HBV associated pancreatitis. Studies reviewed in this section suggest that AP developing post HBV is a rare entity which can be controlled by lamivudine therapy. Nonetheless, that same issue is thoroughly different in transplant context which will be discussed latter in this review article.

NON-A NON-B HEPATITIS/ HEPATITIS C VIRUS

Due to the chronic nature of hepatitis C virus infection, to the best of our knowledge, there is limited data in the current literature supportive of any connection between this infection and development of AP. Nonetheless, there is a case report from a 33-year-old man who developed AP concomitant to non-A non-B hepatitis virus infection [28]. Although no specific diagnostic test was performed at that time, patient’s data suggests that he probably was infected by hepatitis C virus infection. In another case report, Álvares-da-Silva et al. [29] report from a 70-year-old woman presenting with signs and symptoms of icterus and pancreatitis; final diagnosis was acute HCV infection and pancreatitis. She was treated and was asymptomatic at the 10th month after diagnosis. To our knowledge these two reports are the only evidence existing in the literature supportive of any potential role for HCV infection in the development of AP.

HEPATITIS E VIRUS

In the prospective follow up of 54 patients with documented diagnosis of acute hepatitis E virus infection, Jain et al. [14] reported 4(7.4%) cases developed AP in their infection course. In a series of six cases with hepatitis-virus-associated AP, Mishra et al. [15] report a 14-year-old boy presenting with jaundice and severe epigastric pain, after 2 weeks of prodrome. Final diagnosis was acute HEV infection and AP; he received conservative treatment and thoroughly recovered from both conditions. Deniel et al. [30] report a 26-year-old man presented with intense epigastric pain 3 weeks after developing signs and symptoms of acute hepatitis including jaundice which was confirmed as acute HEV infection. Computed tomography confirmed diagnosis of necrotizing pancreatitis grade E in the Ranson-Balthazar radiological classification with a pseudocyst. The patient recovered after conservative management. Another similar case was reported by Somani et al. [31]; a 35-year-old Indian man developed severe epigastric pain after about 1 week of presenting with signs of icterus. Final diagnosis was acute HEV infection and acute necrotizing pancreatitis developing pseudocyst; he developed acute renal failure and hemodynamic instability that led to his demise. Jaroszewicz et al. [32] also report a 28-year-old Pakistani-origin French male patient who represent with icterus and epigastric pain, with final diagnosis of HEV infection and AP; he recovered his disease course with conservative treatment. Makhartia et al. [33] also report from a 45-year-old Indian man who represent with acute HEV infection and AP with benign course. Bhagat et al. [34] report a series of 4 acute HEV-infection related AP in people of Indian ethnicity who completely recovered from their illnesses with medical management. Thapa et al. [35] report an Indian boy as young as 7-year-old with glucose 6 phosphate dehydrogenase deficiency who present with acute HEV infection and AP, which well responded to conservative therapy. Again, literature lacks enough data coming from prospective studies that investigates this issue, and we recommend future tries directing at it, with some focus on genetic specifications of the patients as well as the virus type.

IN TRANSPLANT PATIENTS

AP developing in the context of acute hepatitis virus infection has also been reported in organ transplant recipients. A retrospective study of 1832 liver transplant recipients at a center, 55 (3%) of them had a confirmed diagnosis of AP during their follow up, in 17/114 (14.9%) of them, hepatic failure was due to HBV cirrhosis, 15/340 (4.4%) due to non-A non-B hepatitis, and 1/59 (1.7%) due to autoimmune hepatitis [36]. Cavallari et al. [25] report from a 32-year-old Italian man who developed liver failure due to fulminant HBV infection. After orthotopic liver transplantation, he experienced an acute reactivation of HBV infection which, according to the HBV-DNA load profile, it started on day 40 post-transplantation and reach to its peak level on day 70. On day 60, the patient came with complaint from severe abdominal pain which was finally confirmed as AP diagnosis. The patient died despite intensive treatment [25]. In a series of 5 kidney transplant patients who represented AP after acute viral infections, Sinha et al. [37] report a 49-year-old Indian renal recipient who developed symptoms and signs of AP and acute HEV infection. He also represented with infected pseudocyst which then get drained, and finally died of multiple organ failure. Limited data from the literature review in this section is suggestive of a catastrophic consequence for AP occurring in the context of acute hepatitis in transplant patients; while future studies with large patient populations are needed for more detailed investigations.

AUTOIMMUNE HEPATITIS/PANCREATITIS

Autoimmune involvement of either liver or pancreas has also been reported to be related to the occurrence of the other. Although autoimmune disease may not be considered the same as acute disease, we felt that to have a perfect view on the relation of these two conditions, it is also necessary to discuss autoimmune diseases as well. We found two case reports in the current literature indicating any relation between these two conditions. The second report is from a 44-year-old Brazilian white woman who was a confirmed case of autoimmune hepatitis type 1 and developed AP which had been well managed with conservative treatment [38].
INDUCED BY ANTI-HEPATITIS DRUGS

Drug-induced AP has also been reported in patients with viral hepatitis. In a review of data of 1706 HCV-infected patients under interferon-α2b (IFN) and ribavirin (RBV) therapy in a single center; Chaudhari et al. [39] reported 7 (0.4%) cases (4 males, 3 females; mean age: 51±5 years) who have developed pancreatitis during a mean time of 13.4 months after treatment initiation, which is quite higher than the incidence rate in the general population [40, 41]. IFN and RBV were discontinued in all patients at the time of diagnosis of AP. Six out of the seven patients (85.7%) were hospitalized and one refused hospital admission. Pancreatitis was finally resolved in all seven patients and none of these individuals had recurrent pancreatitis during a median follow-up of 18 months (range, 3–27 months).

There are also some case reports indicating similar effects for pharmaceutical agents in inducing AP. Tahan et al. [42] in a report from a 45-year-old man with chronic hepatitis C virus infection with positive RNA who were put on treatment with IFN-α2b plus RBV, and after 5 weeks of drug therapy, he came with severe epigastric pain indicative of AP. Cessation of pharmaceutical treatment and supportive therapy brought him full recovery, with no recurrence within 1 year of follow-up. A series of two patients with chronic HCV infection who were under therapy with IFN-α2b (and RBV in one case) has been reported by Eland et al. [43] from Netherlands who developed AP. This study is very interesting because of the very meticulous conduct of the authors to their patients that showed details of the pharmaceutical side effects on the development of AP. In the first case, after cessation of both the IFN and RBV which resulted in complete remission of the acute phase pancreatitis; nonetheless, 5 days after hospital admission, IFN was readministered without RBV which resulted in return of the signs and symptoms and laboratory results indicative of the acute illness, just within hours. In the second case, after physical and laboratory evidence for AP following IFN therapy, drug treatment was discontinued and the patients got recovery. Again, treatment was re-administered, and within two and a half hour, serum amylase and lipase levels increased several times, and within 2 weeks, he developed epigastric pain that was confirmed as not related to pancreas [43]. Another case-report by Cecchi et al. [44] described disease course of a 52-year-old Italian Caucasian man who got under treatment with IFN-α2b and RBV for chronic HCV infection just from 8 days before the signs started, which was finally diagnosed as AP. His symptoms were thoroughly remitted just one day after cessation of the pharmaceutical treatment, and no reoccurrence of pancreatitis was observed in a 6 months follow-up.

DISCUSSION

Literature is strongly indicative of associations between hepatic diseases and pancreas injury [45]. Nevertheless, such a relationship is most evident in neoplastic conditions, and most of the literature has focused on this issue [46]. Maybe the second most investigated topic on this extended area of research would be the increased pancreatic enzymes in any liver conditions [47], but a potential relationship between acute hepatitis and AP has not been a matter of concern in the current literature; and we did not find any comprehensive review article systematically searching the literature in our searches, despite extensive efforts. So, we prepared this paper that comprehensively and systematically reviews the existing evidence on potential relationship between acute hepatitis of any type and AP development.

FHF was the first hepatic condition attended in this review article. The existing literature indicates astonishingly high rates of AP (up to 44% [9]) developing in the context of FHF, and this rate was not largely dissimilar in different reports (33% in one survey [10] and 40% in another [11]). So, with the unexpectedly high incidence rate of AP in FHF; it seems very necessary to implement a screening program which puts high levels of alertness for the physicians and the health system. The limitation of our findings in FHF-related AP is mostly related to the very divergent causes of FHF as well as high mortality rate of FHF itself, irrespective of development of an AP course, which might provoke some bias to our findings.

Acute HAV infection has also been repetitively reported as a causative factor in the development of AP. Although most of the evidence on this association comes from case reports and small series; nonetheless, there is one prospective study investigating the rate of AP developing within 4 weeks of the diagnosis of acute HAV; Jain et al. [14] in their study of 124 patients with acute viral hepatitis (16 HAV) have reported 12.5% (2 males) of people who catch acute HAV infection have been diagnosed with AP; within the follow up time. In fact, from 124 patients (94 males, 30 females) diagnosed with acute HAV, HBV and HEV infections, finally 7 (5.6%), all males, developed AP which could be suggestive of a male preponderance in this relation (7 out of 94 (7.4%)). The higher frequency of males (83%) in a series of 6 reported by Mishra et al. [15] could also be confirmative to this conclusion; although in this study, the overall incidence has not been reported. A careful review of the reports from HAV infection and AP development shows that the only cases simultaneously developing both the conditions are females. As well, females seemed to be older than males at the time of diagnosis. In none of the reports or series, any incident mortality has been reported, so we can conclude that AP in the context of HAV infection has a benign course.

The number of reports studying an association between HBV infection and AP is limited. In the prospective study by Jain et al. [14], only one out of 54 (<2%) of the HBV patients developed AP; while in the series report by Yuen et al. [23], 80% of patients with both conditions died of pancreatitis, suggestive of very aggressive and fatal course of AP developing in the course of HBV. Moreover, the study by Chen et al. [27] showed that lamivudine therapy is not only curative in these patients, it also brings remission in cases with recurring episodes of AP.

In the case of acute HCV or non-A non-B hepatitis infection and relation to AP development, data is extremely limited. Nonetheless, both of the cases reported in the literature had a benign course of illness with complete recovery after conservative treatment. On the other hand, data on HEV infection and AP is immensely available. In their prospective study, Jain et al. [14] reported 7.4% of their HEV infected patients developing AP, which hits the highest record among all types of acute viral hepatitis. It also seems that AP after HEV infection is most likely to represent with pseudocysts, with both of the two cases reported with this condition in this review having acute HEV infection. Another interesting observation in HEV related AP is the ethnic predominance in this relation with all cases being from Indian/Pakistani ethnicity.

In transplant recipients also, hepatitis has been associated with AP episodes. In liver transplant recipients, incidence of AP was most high in patients whose hepatic failure was due to HBV infection with about 15% of all patients, followed by non-A non-B hepatitis (4%) and the least frequency for autoimmune non-hepatitis (<2%) [36]. Moreover, it has been shown that development of an AP episode in HBV infected liver transplant recipients is directly associated with the blood HBV-DNA load [25]. An interesting observation in this subsection was that just like patients in non-transplant context, the only transplant recipient who was reportedly developed pseudocyst was infected by HEV infection.

AP induced by pharmaceutical therapy for HCV infection has also been broadly reported in the literature. In a large series, Caudhari et al. [40] reported 0.4% incidence of AP during anti-HCV treatment. Similar observation has also been reported by other authors, as well [43, 45]. Interestingly, evidence suggests that it is IFN and not RBV that induces pancreatitis [45]. Finally AP in the context of IFN therapy seems to be a benign disorder, with full recovery after cessation of the drugs.

CONCLUSION
In conclusion, substantial evidence is suggestive of strong associations between acute hepatitis and AP. Prognosis and features of such a relation is also distinctly associated with the reason of hepatitis. Nonetheless, we should have in mind that this conclusion has been made based on data coming from resources of limited study populations; and therefore, future studies of large patient populations with strong methodological approach are needed for confirming and extending our findings.

Conflict of Interest
Authors declare to have no conflict of interest.

References


