

# Brucellosis-related acute pancreatitis: A rare complication of a universal disease

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## Abstract

**Objectives:** To determine the prevalence and determinants of acute pancreatitis in patients with acute brucellosis.

**Methods:** Adult patients with brucellosis were retrospectively recruited. Brucellosis and acute pancreatitis were diagnosed according to standard criteria. Laboratory analyses included Wright agglutination titre, serum biochemical parameters and blood count.

**Results:** Patients with acute pancreatitis ( $n = 21$ ) had significantly higher Wright agglutination titres, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase,  $\gamma$ -glutamyl transpeptidase, amylase, lipase and serum glucose concentrations, and significantly lower haemoglobin concentrations and haematocrit than patients with brucellosis alone ( $n = 326$ ).

**Conclusions:** Hyperglycaemia, anaemia, and liver transaminase and cholestatic enzyme concentrations may represent new approaches for assessing disease severity in patients with brucellosis and acute pancreatitis.

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## Introduction

Brucellosis is a common zoonotic infectious disease in Turkey and the Middle East.<sup>1</sup> It is characterised by nocturnal fever, hepatosplenomegaly, arthritis and haematological symptoms including leukopenia, and can progress to multisystem organ failure and death (mainly due to sepsis).<sup>2</sup> Human brucellosis is endemic in our region of Turkey, due to consumption of a traditional herbal cheese prepared from unpasteurized fresh milk.<sup>1</sup>

Acute pancreatitis is an infrequent but clinically significant consequence of acute brucellosis, but it is unclear whether such pancreatic injury is due to bacterial involvement or the host immune response.<sup>2-6</sup> Although inflammation is clearly implicated in brucellosis-related pancreatitis,<sup>4</sup> there is limited information regarding pancreatic involvement in brucellosis. The aim of the present study, therefore, was to determine the prevalence of and clinical parameters associated with acute pancreatitis in patients with brucellosis.

## Patients and methods

### Study population

The study retrospectively enrolled adult patients (aged > 17 years) with acute brucellosis attending the Hepatology Clinic, Yuzuncu Yil University, Van, Turkey, between April 2013 and November 2014. Patients with biliary pancreatitis or insufficient follow-up data were excluded from the study. Brucellosis was diagnosed by the presence of appropriate clinical signs and symptoms and at least one of: (i) positive standard tube agglutination test (STA) (titre  $\geq$  1/160); (ii) positive Coombs test

(titre  $\geq$  1/160); (iii) isolation of *Brucella* organisms from cultures of blood, bone marrow, cerebrospinal fluid, other sterile sites, or tissue samples. Clinical and biochemical data were obtained from medical records.

Acute pancreatitis was diagnosed according to the revised Atlanta criteria,<sup>7</sup> and required at least two of: (i) abdominal pain (epigastric pain often radiating to the left flank and the back); (ii) serum amylase and lipase levels at least three times greater than the upper limit of normal; and (iii) characteristic findings on contrast enhanced computed tomography (CT), magnetic resonance imaging or transabdominal ultrasonography. Patients with biliary pancreatitis and with insufficient follow-up information were excluded from the study. All patients were treated with doxycycline 100 mg orally, twice daily, plus rifampin 600–900 mg (15 mg/kg) orally once daily for  $\geq$ 40 days. All participants provided written informed consent for their data to be included in the study. Ethics committee approval was not required due to the retrospective nature of the study.

### Statistical analyses

Data were presented as mean  $\pm$  SD or *n* of patients (%); and between-group comparisons were made using Fisher's exact test. Statistical analyses were performed using SAS<sup>®</sup> software, version 9.1 (SAS Institute, Cary, NC, USA). *P*-values < 0.05 were considered statistically significant.

## Results

The study included 347 patients with acute brucellosis (184 male/163 female; mean age

**Table 1.** Clinical characteristics of patients with acute brucellosis included in a study to determine the prevalence of acute pancreatitis ( $n = 347$ ).

Parameter	Patients without pancreatitis $n = 326$	Patients with pancreatitis $n = 21$	Statistical significance <sup>a</sup>
Sex, male/female	175/151 (53.7/46.3)	9/12 (42.9/57.1)	NS
Age, years	32.9 ± 10.8	45.3 ± 15.6	$P = 0.007$
<i>Brucella</i> antigen, Wright STA titre	335.2 ± 323.6	541.3 ± 447.8	$P = 0.039$
Haemoglobin, g/dl	13.2 ± 2.0 ( $n = 315$ )	11.5 ± 2.4	$P = 0.001$
Haematocrit, %	39.5 ± 6.2 ( $n = 314$ )	34.5 ± 6.9	$P = 0.001$
Platelets, × 10 <sup>3</sup> /μl	260.0 ± 118.6 ( $n = 314$ )	261.6 ± 156.6	NS
Leukocytes, × 10 <sup>3</sup> /μl	7.4 ± 3.1 ( $n = 314$ )	7.5 ± 3.2	NS
ALT, U/l	51.4 ± 145.1 ( $n = 316$ )	447.0 ± 843.7	$P = 0.001$
AST, U/l	75.5 ± 336.6 ( $n = 305$ )	510.6 ± 1243.3	$P = 0.001$
ALP, U/l	277.7 ± 256.2 ( $n = 199$ )	411.4 ± 426.4	$P = 0.036$
GGT, U/l	70.0 ± 105.3 ( $n = 157$ )	153.3 ± 208.5 ( $n = 20$ )	$P = 0.004$
Amylase, U/l	75.0 ± 27.8 ( $n = 178$ )	1778.7 ± 2255.7 ( $n = 20$ )	$P = 0.001$
Lipase, U/l	57.7 ± 81.8 ( $n = 44$ )	1201.3 ± 1261.2 ( $n = 19$ )	$P = 0.001$
Glucose, mg/dl	97.4 ± 31.8 ( $n = 204$ )	191.2 ± 71.1	$P = 0.001$
LDH, U/l	305.2 ± 108.5 ( $n = 6$ )	528.2 ± 374.8 ( $n = 18$ )	NS
Hepatic granuloma	9/74	6/21	$P = 0.009$

Data presented as  $n$  patients (%) or mean ± SD.

NS, not statistically significant ( $P \geq 0.05$ ; Fisher's exact test); ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT,  $\gamma$ -glutamyl transpeptidase; LDH, lactate dehydrogenase.

<sup>a</sup>Fisher's exact test.

33.6 years; age range 17–99 years), of whom 253 (73%) were from rural areas. A total of 21 patients (6.1%) were diagnosed with acute pancreatitis (nine male/12 female; mean age 45.3 ± 15.6 years; age range 21–75 years). Necrotising pancreatitis was diagnosed in two patients (0.6%), who underwent surgical necrosectomy of the pancreas in addition to receiving antibiotic therapy. There were no deaths attributed to brucellosis or pancreatitis during the study period.

Data regarding demographic and clinical characteristics of patients with or without pancreatitis are shown in Table 1. Patients with pancreatitis were significantly older, had significantly higher Wright STA titres, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP),  $\gamma$ -glutamyl transpeptidase

(GGT), amylase, lipase and serum glucose concentrations, and significantly lower haemoglobin concentration and haematocrit than patients without pancreatitis ( $P < 0.05$  for all comparisons; Table 1). The presence of pancreatitis was not associated with platelet or leukocyte counts, or lactate dehydrogenase (LDH) concentration.

Abdominal CT revealed the presence of hepatic granuloma in 15/95 patients (15.8%). Patients with pancreatitis were significantly more likely to have hepatic granuloma than those without ( $P = 0.009$ ).

## Discussion

Bacterial, viral and parasitic infections can cause acute pancreatitis,<sup>8,9</sup> and the pancreas

interacts with (and responds to) pathogens in several ways, including activation of dendritic cells, macrophages, fibroblasts and T cells.<sup>10</sup> The rate of acute pancreatitis among patients with brucellosis was 6.1% in the present study. Of these, two patients (0.6%) had necrotising pancreatitis. It appears that acute brucellosis is associated with increased risk of oedematous pancreatitis in this patient population.

The hepatobiliary system is often involved in acute brucellosis. Hepatitis is the most common liver disorder,<sup>11</sup> and elevated liver transaminase levels may be seen at initial presentation.<sup>11</sup> Liver abscess, jaundice and granuloma are occasionally present, as well as cholecystitis and hepatosplenomegaly.<sup>11–14</sup> The effects of brucellosis on the pancreas were first reported in 1989,<sup>15</sup> but there have been few case reports of brucellosis-related pancreatitis,<sup>15–17</sup> and, to the best of our knowledge, no data regarding the incidence of pancreatitis in patients with brucellosis.

The natural history of acute brucellosis-related pancreatitis is poorly understood, and it is important to determine which patients are at greatest risk of progression to pancreatitis. Acute pancreatitis was associated with elevated serum Wright agglutination titres in the present study. Cholestasis enzymes are biomarkers for cholestatic disease, and elevated ALP and GGT are associated with acute pancreatitis.<sup>18</sup> A study performed in Turkey detected cholestasis in 66.1% of patients with brucellosis.<sup>11</sup>

Hyperglycaemia, anaemia, elevated liver transaminase and cholestatic enzyme concentrations were associated with acute pancreatitis in patients with brucellosis in the present study and may be useful in the diagnosis of *Brucella*-related acute pancreatitis. On the other hand, LDH concentrations, leukocyte and platelet counts were similar in patients with and without pancreatitis. An elevated leukocyte count is a predictor of severe pancreatitis, but

brucellosis is known to be associated with bone marrow cytophagocytosis.<sup>19</sup> This suggests that the leukocyte count should not be used as a marker of severity in brucellosis-related pancreatitis.

Hepatic granuloma is associated with brucellosis,<sup>20</sup> and the rate of hepatic granuloma was 15.8% in the present study, occurring significantly more frequently in patients with pancreatitis compared with those with brucellosis alone. Hepatic granuloma (as a sign of severe brucellosis) may predict acute pancreatitis in these patients.

The present study is limited by its retrospective nature, which meant that it was not possible to examine patients for the effect of treatment on prognosis.

In conclusion, hyperglycaemia, anaemia, and liver transaminase and cholestatic enzyme concentrations may represent new approaches for assessing disease severity in patients with brucellosis and acute pancreatitis. Further studies of acute brucellosis would lead to a better understanding of the development of acute pancreatitis.

### Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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### References

1. Yumuk Z and O'Callaghan D. Brucellosis in Turkey – an overview. *Int J Infect Dis* 2012; 16: e228–235.
2. Pappas G, Akritidis N, Bosilkovski M, et al. Brucellosis. *N Engl J Med* 2005; 352: 2325–2336.
3. Dulger AC, Aslan M, Ceylan MR, et al. The syndrome of inappropriate secretion of antidiuretic hormone in patients with

- brucellosis. *J Clin Lab Anal* 2014. doi: 10.1002/jcla.21780. [Epub ahead of print].
4. Papaioannides D, Korantzopoulos P, Sinapidis D, et al. Acute pancreatitis associated with brucellosis. *JOP* 2006; 7: 62–65.
  5. Belo AC, Grabowski EW, Zhang C, et al. Case of chronic pancreatic brucellosis presenting as hemossuccus pancreaticus. *JOP* 2007; 8: 429–432.
  6. Berber I, Erkurt MA, Yetkin F, et al. A rare disease in the differential diagnosis of acute pancreatitis: acute brucellosis. *Intern Med* 2014; 53: 2401–2404.
  7. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62: 102–111.
  8. Topazian M and Gorelick FS. Acute pancreatitis. In: Yamada T, Alpers DH, Kaplowitz N, Laine L, Dwyang C, Powell DW (eds) *Textbook of Gastroenterology*, 4th ed. Philadelphia, USA: Lippincott Williams and Wilkins, 2003, pp.2026–2061.
  9. Parenti DM, Steinberg W and Kang P. Infectious causes of acute pancreatitis. *Pancreas* 1996; 13: 356–371.
  10. Granger J and Remick D. Acute pancreatitis: models, markers, and mediators. *Shock* 2005; 24(Suppl 1): 45–51.
  11. Ozturk-Engin D, Erdem H, Gencer S, et al. Liver involvement in patients with brucellosis: results of the Marmara study. *Eur J Clin Microbiol Infect Dis* 2014; 33: 1253–1262.
  12. Ariza J, Pigrau C, Canas C, et al. Current understanding and management of chronic hepatosplenic suppurative brucellosis. *Clin Infect Dis* 2001; 32: 1024–1033.
  13. Cervantes F, Bruguera M, Carbonell J, et al. Liver disease in brucellosis: A clinical and pathological study of 40 cases. *Postgrad Med J* 1982; 58: 346–350.
  14. Andriopoulos P, Tsironi M, Deftereos S, et al. Acute brucellosis: presentation, diagnosis, and treatment of 144 cases. *Int J Infect Dis* 2007; 11: 52–57.
  15. al-Awadhi NZ, Ashkenani F and Khalaf ES. Acute pancreatitis associate with brucellosis. *Am J Gastroenterol* 1989; 84: 1570–1574.
  16. Alemán MC, Alegre J, Marqués A, et al. [Acute pancreatitis in the course of brucellosis]. *An Med Interna* 1994; 11: 311. [in Spanish, English Abstract].
  17. Odeh M and Oliven A. Acute pancreatitis associated with brucellosis. *J Gastroenterol Hepatol* 1995; 10: 691–692.
  18. Telem DA, Bowman K, Hwang J, et al. Selective management of patients with acute biliary pancreatitis. *J Gastrointest Surg* 2009; 13: 2183–2188.
  19. García P, Yrivarren JL, Argumans C, et al. Evaluation of the bone marrow in patients with brucellosis. Clinico-pathological correlation. *Enferm Infecc Microbiol Clin* 1990; 8: 19–24. [In Spanish, English abstract].
  20. Albayrak A and Albayrak F. Hepatic granulomas associated with brucellosis: Hepatic granulomas and brucellosis. *Hepat Mon* 2011; 11: 1–2.