Morphological study of the relation between accidental hypothermia and acute pancreatitis

ALAN K FOULIS

From the Department of Pathology, Western Infirmary, Glasgow

SUMMARY There is a recognised but poorly understood association between hypothermia and acute pancreatitis. A histological study of the pancreas was made in eight patients with accidental hypothermia who had evidence of pancreatitis at necropsy. From an analysis of the patterns of parenchymal necrosis in the pancreas it was thought that there were at least three possible mechanisms for the relation between hypothermia and pancreatitis. Firstly, that ischaemic pancreatitis may result from the "microcirculatory shock" of hypothermia. Secondly, that both hypothermia and pancreatitis may be secondary to alcohol abuse; and finally, that severe pancreatitis may be the primary disease and that hypothermia results from the patients' social circumstances.

Acute pancreatitis is recognised to be a common finding in adult patients with accidental hypothermia. Between 50% and 65% of hypothermic patients have a raised serum amylase activity, and acute pancreatitis is found at necropsy in 20-30% of cases.^{1,2} The mechanisms involved in this relation have remained obscure.

Recent work by the author has shown that at least two basic factors are involved in the initiation of acute pancreatitis, and that these can be recognised on histological examination of the pancreas.³ "Periductal" necrosis, where there is inflammation of pancreatic excretory ducts with inflammation and necrosis of surrounding parenchyma, was associated with pancreatitis secondary to gallstones, alcohol abuse and diabetes. "Perilobular" necrosis, where necrosis is confined to the microcirculatory periphery of the pancreatic exocrine lobule, was associated with pancreatitis occurring secondary to either septic or cardiogenic shock and was thought to represent ischaemic pancreatitis. While either of these patterns of necrosis can be found as the sole manifestation of pancreatitis, periductal necrosis may result in damage to adjacent vessels, which then thrombose. Such thrombosis will result in sludging in the microcirculation and thus perilobular necrosis. Therefore when both periductal and perilobular necrosis are found together periductal necrosis is presumed to represent the initial event.

This paper presents the clinical findings and patterns of pancreatic necrosis seen in eight patients with pancreatitis and accidental hypothermia. On the basis of these findings an attempt is made to explain the mechanisms involved in their relation.

Material and methods

The necropsy records of the Western Infirmary and Southern General Hospital, Glasgow, over the last five years, were studied. Cases were selected where the patient had been admitted with a clinical diagnosis of hypothermia (rectal temperature less than 35°C, using a low reading thermometer), where there was clinical and/or post mortem evidence of acute pancreatitis, and where advanced autolysis did not preclude adequate microscopic examination. Eight cases were suitable for study. Sections of pancreas were stained by haematoxylin and eosin and Martius scarlet blue.

Results

The results are summarised in Table 1. In only case 2 was a serum amylase estimation performed and a diagnosis of pancreatitis made antemortem.

Macroscopic pancreatitis was noted at necropsy in all but cases 5 and 6. In case 8 there was widespread fat necrosis in the lesser and greater peritoneal sacs. Otherwise necrosis was confined to the immediate vicinity of the pancreas. The thyroid was normal macroscopically in all but case 3 where the thyroid was atrophic. In cases 5 and 8 histology was done which confirmed a normal thyroid morphology. Biochemical thyroid function tests were done in cases 1, 2 and 3. The former two were euthyroid and the latter hypothyroid.

In cases 1-5 perilobular necrosis of the pancreas was the only pattern observed (Fig 1). In cases 1 and 2 there was marked congestion and interstitial haemorrhage, maximal at the periphery of the lobules. This was

Hypothermia and acute pancreatitis: clinico-pathological summary

Case No	Age (yr) and sex	Admission temperature (°C)	Admission heart rate (beats/min)	Admission BP (mmHg)	Interval between hypothermia and death	Possible predisposing factors for hypothermia	Gallstones at necropsy	Pattern of pancreatitis necrosis	Presumed cause of death and other relevant findings at necropsy
1	85 M	26	40	Unrecordable	2 days	Nil	No	Perilobular	Bronchopneumonia
2	64 F	27	62	Unrecordable	2 days	Alcohol abuse	No	Perilobular	Bronchopneumonia
3	80 F	34	58	70/50	2 wks	Myxoedema	Yes	Perilobular	Coronary thrombosis and myocardial infarction
4	69 F	32	60	110/70	2 wks	Parkinson's disease	No	Perilobular	Boundary zone cerebral infarct approx two weeks duration
5	79 F	28	60	Unrecordable	5 days	Nil	No	Perilobular	Bronchopneumonia
6	56 M	34	Not known	Not known	2 days	Alcohol abuse	No	Periductal	Myocardial infarction. Small bowel infarction
7	51 M	29	60	Unrecordable	1 day	Alcohol abuse	No	Perilobular and periductal	Peripheral vascular disease
8	88 F	32	120	Unrecordable	2 days	Nil	Yes	Perilobular and periductal	Pulmonary emboli

associated with fibrin deposition both within capillaries and in their immediate vicinity (inset at higher magnification). In cases 3 and 4 there was evidence of organisation of the necrotic pancreatic parenchyma at the lobular periphery. Cases 6, 7 and 8 had periductal necrosis associated with marked duct inflammation (Fig 2). Significant perilobular necrosis was also seen in cases 7 and 8.

Several clinical factors were present which can be associated with the development of pancreatitis. Gallstones, confined to the gallbladder, were present in two patients. Three patients were known to be chronic alcoholics and six patients were shown to be hypotensive on admission. Five patients had been prescribed drugs prior to admission. Cases 5 and 8 were taking frusemide, case 1 cyclopenthiiazide, case 3 bendrofluzide and case 4 orphenadrine hydrochloride.

Discussion

Perilobular necrosis, when it is the sole pattern of parenchymal necrosis has been shown previously to represent ischaemic pancreatitis.³ The patients in that study had a high incidence of systemic hypotension and four of the five patients in this study who had only perilobular necrosis were hypotensive on admission. The fifth patient (case 4) had an admission blood pressure of 110/70 mmHg. However she was a known hypertensive, who at a recent admission had a blood pressure of 190/105 mmHg. Thus all five patients had relative hypotension.

It has been argued that the changes in the microcirculation during hypothermia resemble those in shock, and consist of a loss of microcirculatory control with hyperfusion.⁴ In severe hypothermia local accumulation of metabolites and hypoxia in the microcirculation result in loss of arteriolar and precapillary sphincter tone. The venous side of the microcirculation is thought to be

less susceptible to these factors and thus the capillaries become engorged with stagnant blood and the patient develops hypotension. Fluid and red cells leak out of the circulation when the capillary endothelium is damaged by hypoxia. This results in the tissue appearance of engorged capillaries, haemorrhage into the interstitial space and intra and extra vascular coagulation. This was exactly the appearance seen in the periphery of the pancreatic lobules in patients one and two who both died within two days of the hypothermic episode. Thus it appears that in the first five patients, who had only perilobular necrosis, with no evidence of duct inflammation, the pancreatitis was secondary to the "microcirculatory shock" of primary hypothermia. It could be argued that case 2 was alcoholic and case 3 had gallstones and that these could be the causes of the pancreatitis. However, previous studies have shown no association between perilobular necrosis as the sole form of pancreatitis and these causes of pancreatitis.³

Ischaemic damage to the pancreas as a result of hypothermia has been previously suggested as a cause of pancreatitis. Two case reports suggested that hypothermia had caused intravascular coagulation and that this had precipitated ischaemic pancreatitis. The patient studied by Savides and Hoffbrand⁵ had thrombosis of the superior pancreaticoduodenal vein and intrapancreatic veins, in addition to infarction of areas of the gallbladder, duodenum and both adrenals. The second patient, reported by Mahood and Evans⁶ had both haematological and post mortem evidence of disseminated intravascular coagulation (DIC). Neither patient was hypotensive on admission. Activation of the coagulation system is a recognised occurrence in patients with accidental hypothermia,⁷ but DIC is also a recognised complication of acute pancreatitis.⁸ Thus it is difficult to decide whether pancreatitis or hypothermia caused the intravascular coagulation. The finding of pancreatic duct inflammation reported in Savides and Hoffbrand's patient

Fig. 1 This is from case 2 (left). Note that the pancreatic parenchymal necrosis is confined to the periphery of the lobules. Haematoxylin and eosin $\times 40$. Inset (right) Strands of fibrin can be seen surrounding acini. Fibrin deposition was maximal at the periphery of lobules. Martius scarlet blue $\times 240$.

Fig. 2 This is from case 8. Inflamed intralobular ducts containing proteinaceous concretions are marked by arrows. There is surrounding periductal inflammation and necrosis. Haematoxylin and eosin $\times 150$.

would be unusual in an ischaemic pancreatitis and might suggest that pancreatitis was the initial event. Similarly, in Mahood and Evans' report, where no details of the pancreatic morphology are given, the patient was an alcoholic who could have developed primary alcoholic pancreatitis. Thus in both cases the exact sequence of events is still in doubt.

Cases 6, 7 and 8 had duct inflammation and periductal necrosis. This form of pancreatitis has been associated with alcohol abuse or the presence of gallstones. Both cases 6 and 7 were alcoholic and case 8 had gallstones. Chronic alcoholism predisposes a patient to accidental hypothermia⁹ and it may be that in case 6, who had only microscopic pancreatitis, with no evidence of periductal necrosis, both hypothermia and pancreatitis were secondary to alcohol abuse. Case 8 had the most extensive pancreatitis of the group. On admission she was noted to have a distended silent abdomen and a tachycardia. The histological appearance of widespread periductal necrosis is entirely consistent with a gallstone aetiology for the pancreatitis and is not seen in pancreatitis secondary to shock. Thus here it is likely that the patient had primary gallstone pancreatitis and developed hypothermia as a result of exposure (she lived alone and was found unconscious on the floor of her flat). In case 7 the presence of duct inflammation and periductal necrosis is strongly suggestive of an alcoholic aetiology for the pancreatitis. Whether the hypothermia was secondary to alcohol abuse as suggested in case 6, or pancreatitis as suggested in case 8 remains a moot point.

Four of the patients studied were receiving diuretics.

By 1977 pancreatitis had been reported in 16 patients treated with these drugs in whom no other cause for the pancreatitis was apparent.¹⁰ Considering the high prevalence of diuretic usage this is obviously a very rare association, and a causal role for diuretics has not yet been fully established. In the present study other predisposing factors were present which correlated with the morphological appearances in the pancreas, so a drug aetiology for the pancreatitis seems unlikely.

Conclusion

Three possible mechanisms for the relation between accidental hypothermia and pancreatitis in this series are proposed. In cases 1–5 hypothermia appears to have been primary. They have developed the "microcirculatory shock" of hypothermia, which has resulted in ischaemic pancreatitis. In case 6 both the pancreatitis and hypothermia appear to have been the result of alcohol abuse, and in case 8 it seems likely that hypothermia developed secondary to primary gallstone pancreatitis. It will require a larger series based on these lines to determine the relative frequencies of these various mechanisms in the relation between accidental hypothermia and acute pancreatitis.

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The October 1982 issue

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Enzyme-linked immunosorbent assay (ELISA) for detection of specific IgA antibodies to mumps virus B HALEVY, I SAROV

Rapid enzyme-linked immunosorbent assay (ELISA) for *Aspergillus fumigatus* antibodies MD RICHARDSON, JUDITH M STUBBINS, DW WARNOCK

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