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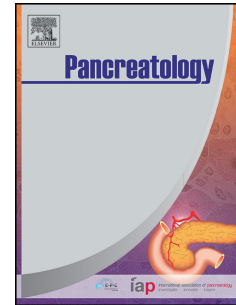
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The sentinel acute pancreatitis event hypothesis revisited

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Dear Editor,

We read with interest the paper from Hori et al. on the frequency of acute pancreatitis (AP) preceding chronic pancreatitis (CP)[1]. In a retrospective analysis, the authors found that only half of patients with 'classical CP' had a preceding history of AP and only half of AP cases had more than one attack (i.e. recurring pancreatitis (RAP)). These findings challenge the sentinel AP hypothesis, which suggests that CP is preceded by a sentinel attack of AP causing infiltration of inflammatory cells and activation of stellate cells, with subsequent ongoing injury or stress promoting fibrosis [2]. Although the authors have to be acknowledged for the impressive sample size for a monocentre study and rigorous research methodology, a few aspects warrant further attention [1]. First, the authors did not consider disease aetiology in their analysis of differences in clinical profiles between CP patients with and without preceding AP. Differing aetiologies have been associated with different clinical phenotypes, which is particularly evident for smoking and alcohol as recently shown in a study from our group [3]. Second, no multivariate analysis was undertaken, which precludes inference of the interrelations between variables.

We attempted to replicate their findings in a cohort of 334 patients with CP and to corroborate the investigation by including disease aetiology and a multivariate analysis approach. Patients were enrolled at two tertiary referral centres in Denmark and classified according to the same criteria used in the study by Hori et al. In our cohort, 180 out of 334 patients had a prior history of AP, which corresponds to a prevalence of 54%. Of patients with preceding AP, 63 (35%) had a single episode of AP and 117 (65%) had RAP. On univariate analysis, age at diagnosis ($p < 0.001$) and the proportion of patients with pain ($p = 0.003$) differed significantly between groups with and without preceding AP (Table 1). Multivariate analysis confirmed the significance and independence of these findings *viz.* age at diagnosis (coefficient = -0.04 , $p < 0.001$) and pain (coefficient = 0.42 , $p = 0.06$), with an additional association observed for exocrine pancreatic insufficiency (coefficient = -0.42 , $p = 0.05$).

Taken together, our findings replicate the study by Hori et al. and underline that only half of patients with CP have a prior history of *clinical evident* AP (single episode or RAP) [1]. Interestingly, a higher proportion of patients with a preceding history of AP or RAP seem to present with a primary symptom of pain at a younger age compared to their counterparts with no history of AP. As the prevalence of alcohol and smoking aetiologies were proportionate between patient subgroups it is not likely that the observed differences were explained by the underlying disease aetiology.

sentinel AP event hypothesis, as they found it difficult to comprehend subclinical AP as an explanation for the absence of clinical attacks of AP [1]. While this argument certainly has merit from a clinical standpoint and is supported by findings from basic studies [4], we propose an alternative explanation for the observed findings. Hence, inter-individual differences in pain sensitivity is a well-known phenomenon and this has been investigated across a wide variety of pain patients and healthy populations [5,6]. The underlying mechanisms are diverse and a number of genetic polymorphisms have been identified [7]. Such differences in pain sensitivity may explain why some patients experience symptomatic AP prior to the development of CP and some do not, even though the underlying disease processes may be similar. This hypothesis is supported by the differences in clinical profiles between patient subgroups in our and the Hori et al. data, although the cross-sectional nature of the studies precludes any definitive conclusions. Importantly, pain sensitivity on the individual patient's level can be examined by quantitative sensory testing and this technique may be used to test if CP patients with and without preceding episodes of AP have different pain sensitivity [8].

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Table 1. Comparison of chronic pancreatitis patients who did or did not have acute pancreatitis (AP) or recurring acute pancreatitis (RAP) preceding chronic pancreatitis (CP) (n=334)

	No preceding AP (n=154)	Preceding AP		P-value
		Single AP episode (n=63)	RAP (n=117)	
Mean age, years	57.8±12.2	54.0±11.8	50.6±12.2	<0.001
Male sex, n (%)	104 (68)	47 (75)	87 (74)	0.38
Alcoholic aetiology, n (%)	126 (82)	53 (84)	98 (84)	0.88
Smoking aetiology, n (%)	93 (60)	46 (73)	81 (69)	0.13
EPI, n (%)	92 (60)	37 (59)	60 (51)	0.35
Diabetes, n (%)	74 (48)	25 (40)	42 (36)	0.12
Pain, n (%)	75 (49)	36 (57)	81 (69)	0.003

EPI: exocrine pancreatic insufficiency