



AALBORG UNIVERSITY
DENMARK

Aalborg Universitet

The sentinel acute pancreatitis event hypothesis revisited

Olesen, Søren Schou; Drewes, Asbjørn Mohr; Novovic, Srdan; Nøjgaard, Camilla

Published in:
Pancreatology

DOI (link to publication from Publisher):
[10.1016/j.pan.2019.03.007](https://doi.org/10.1016/j.pan.2019.03.007)

Creative Commons License
CC BY-NC-ND 4.0

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Olesen, S. S., Drewes, A. M., Novovic, S., & Nøjgaard, C. (2019). The sentinel acute pancreatitis event hypothesis revisited. *Pancreatology*, 19(4), 614-615. <https://doi.org/10.1016/j.pan.2019.03.007>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- ? Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- ? You may not further distribute the material or use it for any profit-making activity or commercial gain
- ? You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

The sentinel acute pancreatitis event hypothesis revisited

Søren Schou Olesen, Asbjørn Mohr Drewes, Srdan Novovic, Camilla Nøjgaard

PII: S1424-3903(19)30087-0

DOI: <https://doi.org/10.1016/j.pan.2019.03.007>

Reference: PAN 1013

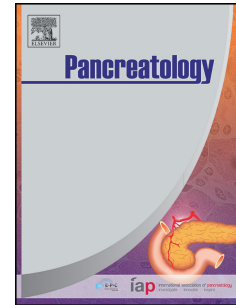
To appear in: *Pancreatology*

Received Date: 4 March 2019

Accepted Date: 31 March 2019

Please cite this article as: Olesen SørSchou, Drewes AsbjørMohr, Novovic S, Nøjgaard C, The sentinel acute pancreatitis event hypothesis revisited, *Pancreatology* (2019), doi: <https://doi.org/10.1016/j.pan.2019.03.007>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



The sentinel acute pancreatitis event hypothesis revisited

Søren Schou Olesen^{1,2}, Srdan Novovic³, Camilla Nøjgaard³ and Asbjørn Mohr Drewes^{1,2}

¹ Centre for Pancreatic Diseases, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark

² Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

³ Department of Gastroenterology, Hvidovre University Hospital, Copenhagen, Denmark

Corresponding author:

Søren Schou Olesen, MD, PhD

Centre for Pancreatic Diseases, Department of Gastroenterology and Hepatology,
Aalborg University Hospital, Mølleparkvej 4, 9000 Aalborg, Denmark

Telephone: +45 99326243, Fax: +45 99326507

E-mail: soso@rn.dk

Acknowledgements

Declaration of personal interests: None

Declaration of funding interests: None

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].

References

- [1] Hori Y, Vege SS, Chari ST, Gleeson FC, Levy MJ, Pearson RK, et al. Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study. *Pancreatology* 2019. doi:10.1016/j.pan.2019.02.004.
- [2] Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. *Pancreatology* n.d.;16:218–24. doi:10.1016/j.pan.2016.02.001.
- [3] Olesen SS, Nøjgaard C, Poulsen JL, Haas SL, Vujasinovic M, Löhr M, et al. Chronic Pancreatitis Is Characterized by Distinct Complication Clusters That Associate With Etiological Risk Factors. *Am J Gastroenterol* 2019. doi:10.14309/ajg.000000000000147.
- [4] Sahin-Tóth M, Hegyi P. Smoking and Drinking Synergize in Pancreatitis: Multiple Hits on Multiple Targets. *Gastroenterology* 2017;153:1479–81. doi:10.1053/j.gastro.2017.10.031.
- [5] Skovbjerg S, Jørgensen T, Arendt-Nielsen L, Ebstrup JF, Carstensen T, Graven-Nielsen T. Conditioned Pain Modulation and Pressure Pain Sensitivity in the Adult Danish General Population: The DanFunD Study. *J Pain* 2017;18:274–84. doi:10.1016/j.jpain.2016.10.022.
- [6] Vaegter HB, Graven-Nielsen T. Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. *Pain* 2016;157:1480–8. doi:10.1097/j.pain.0000000000000543.
- [7] Olesen AE, Nielsen LM, Feddersen S, Erlenwein J, Petzke F, Przemek M, et al. Association Between Genetic Polymorphisms and Pain Sensitivity in Patients with Hip Osteoarthritis. *Pain Pract* 2018;18:587–96. doi:10.1111/papr.12648.
- [8] Kuhlmann L, Olesen SS, Olesen AE, Arendt-Nielsen L, Drewes AM. Mechanism-based pain management in chronic pancreatitis - is it time for a paradigm shift? *Expert Rev Clin Pharmacol* 2019;12:249–58.

ACCEPTED MANUSCRIPT

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