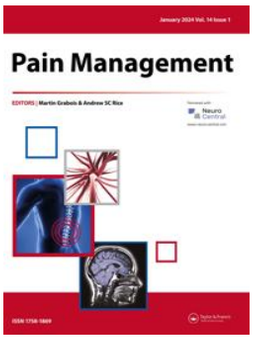

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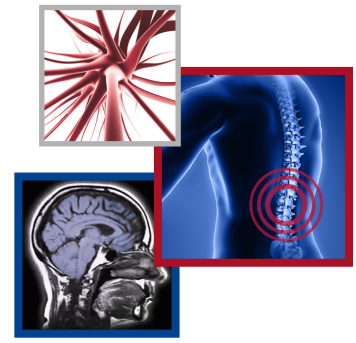

Pain in chronic pancreatitis: mechanics or molecules?

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> "One of the most important premises in treating patients with CP-associated pain is to identify those patients who have not yet progressed into a mechanically unamenable disease."

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Pain due to chronic pancreatitis (CP) is notorious for being problematic both for the patients and the treating clinicians. It can exhibit variable patterns with regard to frequency, duration and localization; strongly varying in its response to therapy [1]. Pain due to CP is now widely recognized to have a neuropathic trait and to be a part of a complex pancreatic neuropathic syndrome [2–5]. Like several visceral pain conditions but also other chronic neuropathic disorders, the mechanisms of pain due to CP have not yet been fully understood [6]. Moreover, it is questionable if we will ever fully understand the complex molecular pathomechanism behind chronic pancreatic pain.

Long-standing pancreatic pain results in multiple morphological and biochemical adaptations both in the peripheral and CNS [7–9]. These neuroplastic alterations include hypertrophy of intrapancreatic nerves [2,10] and severe perineural inflammation of nerves within the pancreas ('neuritis') [11]. These peripheral alterations are accompanied by morphological and functional alterations in brain areas that are responsible for processing of visceral pain, such as, the insular cortex or the anterior cingulate areas [12]. This brain plasticity is believed to be linked to impairment of patients' daily activities and performance, to trigger depression and to result in a neurodegeneration-like state [12].

The burning question, when it comes to chronic pain, regardless of pancreatic or nonpancreatic origin, is in which cases and when the threshold for reversibility and treatability will be reached. In some cases, severe progressive chronic inflammation in the pancreas results in the above mentioned multiple central and peripheral alterations, rendering any type of treatment, be it medical, endoscopic or surgical, ineffective in the long term [4]. Thus, when trying to define the best pain treatment options for patients with CP, it is imperative to correctly identify the actual disease stage of each patient.

Looking at the problem from its very beginning, inflammation in the pancreas can manifest as a diffuse microscopic disease, or lead early on to obstruction of some small- or large-calibre ducts. Indeed, some CP patients present with profound enlargement of the pancreatic head, which is a hotbed of inflammation for many CP patients [13]. On the other hand, other patients have a diffuse small-duct disease, which is not accompanied by such a segmental enlargement of the pancreas. Interestingly, there are geographic differences with regard to the presence of such an inflammatory pancreatic head mass versus small duct/diffuse disease. For example, mid-Europe patients seem to more frequently exhibit an inflammatory pancreatic head mass than, for example, US or northern European patients [14]. For this reason, traditionally, pancreatic head resecting procedures (e.g., Beger or Büchler–Bern) have been developed and more frequently used in mid-Europe when compared with the more frequent usage of lateral draining procedures (e.g., Partington–Rochelle procedure) in the USA [14].

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In addition to stones, an inflamed, enlarged pancreatic head is nearly always accompanied by an outflow obstruction of the pancreatic duct from the pancreatic body and tail. Surgical removal of the pancreatic head, be it in a duodenum-preserving or nonpreserving manner, results in the amelioration of this outflow obstruction and is believed to be one of the leading 'mechanical' factors contributing to the relief of pain [15]. Another important factor is the removal of the pancreatic head as the most richly innervated part of the organ [16]. Thus, removal of the pancreatic head in such cases of inflamed pancreatic head mass may be beneficial due to improvement of the outflow obstruction and to the removal of the pathologically enlarged nerves.

Such a mechanical relief seems to be best achieved by surgery due to its radical nature and there is also some evidence for potential effectiveness of some endoscopic measures such as pancreatic duct stenting, extracorporeal shock wave lithotripsy (ESWL) or sphincterotomy [17]. Still, as clearly shown in several randomized controlled trials [18], surgery should therefore be considered early for CP patients with mechanically amenable disease [18–21]. As such, the most extreme example of a mechanical intervention, total pancreatectomy with islet autotransplantation, results in durable pain relief reaching 82% at 10 years and 90% at 15 years [22]. However, the insulin independence rates at 10 years are still only approximately 20% [22]. With the improvement of endoscopic interventions in the future, it is imaginable that endoscopic interventions as part of a step-up approach [23] may also become effective. However, the long-term success of surgical management for managing pain is clearly superior to endoscopic interventions [24].

One of the most important premises in treating patients with CP-associated pain is to identify those patients who have not yet progressed into a mechanically unamenable disease. As typical for advanced neuropathic syndromes, recurrent attacks of inflammation and repeated bouts of pain change the CNS in such a way that CNS perpetuates pain at some point independently of the peripheral original trigger. The state of progression of chronic pain in CP patients seems to be detectable by means of elegant neurological testing modalities such as quantitative sensory testing, pressure or thermal stimuli, functional magnetic resonance imaging or EEG testing [25]. Such pain phenotyping algorithms in CP patients may be very useful in identifying those patients with very advanced stage, who will not benefit from mechanical interventions.

An unresolved mechanical problem in the pancreas is thus likely to perpetuate the severe neuropathic pain via molecular adaptations in the pancreas, in the peripheral pancreatic nerves, but also in the CNS. Although we do not know the exact neurotransmitter or neurochemical alterations that take place in the brain or in the pancreas of very advanced CP patients, studies on the neurochemical code of the pancreatic nerves of patients whose inflammatory pancreatic head mass has been surgically resected, have taught us a lot about which molecules may be most relevant in this process of pain perpetuation [9,26–28]. As such, increased presence of neurotrophic factors such as nerve growth factor [29], neurturin [9], artemin [26], of proteases [30] and the protease-activated receptors [31], some neuronal enzymes such as neuronal nitric oxide synthase [28], mechanoreceptors [32], ion channels [33,34] or altered glutamatergic signalling [35] emerged as the most likely candidates representing the molecular actors behind the severe, CP-associated pain. It is thus imaginable that designing clinical trials that target these altered neurochemical agents may also yield clinically beneficial results for patients with advanced CP.

The main take for the clinical practice seems to identify patients, who may benefit from mechanical intervention, as early as possible. In fact, advanced CP in the pancreatic head may lead to stenosis of the portal vein and into consequent portal hypertension with multiple venous collaterals [36]. Performing surgery on such patients is linked to much higher morbidity and mortality [36]. Accordingly, early surgery is now recommended as the preferred mode of a treatment for patients with the corresponding mechanical problem in their pancreas [19], resulting in a significant reduction of the opioid need in the most recent randomized control trial [21].

Prior to or after the surgical, medical or endoscopic intervention, CP patients remarkably benefit from avoidance of aggravating factors such as nicotine and alcohol [37]. This fact underlines that ongoing microscopic inflammation of the pancreas represents the main trigger for this severe neuropathic pain syndrome. Therefore, identifying the molecular mechanisms behind the generation of pancreatic pain continues to be of paramount importance. Until the advent of the results from future molecular therapy trials, we need to identify patients at the mechanical stage of the disease, before it turns into a complex neurochemical disaster.

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