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General discussion

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ACNES

Anterior Cutaneous Nerve Entrapment Syndrome (ACNES) is characterized by abdominal pain in a fingertip small area of the abdominal wall that is often accompanied by a specific set of symptoms such as somatosensory disturbances of the skin, hypersensitivity to pinching of the abdominal wall and Carnett's sign (attenuated pain whilst simultaneously pressing and flexing the abdominal muscles).[1] A nerve block with a local anesthetic in the point of maximum pain almost always provides (temporary) relief.[2] As almost always observed in a syndrome, ACNES is in essence an observation of consistently linked associated symptoms and outcomes.

Previous research in this field focused on developing adequate diagnostic tools to identify ACNES patients from, for example, patients with irritable bowel syndrome (IBS) or functional abdominal complaints and evaluating existing therapies in a placebo-controlled fashion.[3,4] These studies resulted in increased awareness of the disease in the Netherlands and subsequently led to augmented flows of potential ACNES patients. Patients were occasionally indeed freed from an erroneous diagnosis and often responded well to new treatments including injection therapy and a neurectomy. These developments fueled exciting prospects for patients who were previously suffering from poorly understood abdominal pain.

Obviously, not all these previously misdiagnosed patients do have ACNES. A reviewer of one of our manuscripts argued that alternative diagnoses, namely psychogenic abdominal disorder, central hyperalgesia conditions or neurological diseases of peripheral nerves or roots may be missed or overlooked in the diagnostic process. Visceral pathologies such as endometriosis, abdominal wall hernias or malignancies are less likely to attribute to the present thesis' patient series as most individuals had extensive work-up before they visited our referral center.

It is probably not inappropriate, however, to call ACNES a 'diagnosis per exclusionem', as is also the case with IBS. Abdominal pain has a variety of causes, and some might even be accompanied with somatosensory disturbances resembling ACNES.[5] On the other hand, ACNES patients can experience 'classic' visceral complaints such as bloating, nausea or ructus.[6] Furthermore, some patients only have few major and minor diagnostic criteria pointing towards ACNES. These 'atypical' patients, however, might still respond favorably to a symptomatic treatment, which makes it only more difficult to interpret results.[7] Is this response a placebo-effect, or does ACNES have a variable phenotype? Conversely, do patients who are not experiencing any benefit from last treatment resorts such as dorsal root ganglion stimulation just do not have ACNES? In the work presented in this thesis, these questions are not entirely answered, yet the syndrome does gain more shape.

Is the pain associated with ACNES a type of neuropathic pain? If one embraces its proposed etiology, the answer is yes. Applegate´s entrapment theory entails that ACNES

should be in the same category as carpal tunnel syndrome, thoracic outlet syndrome, meralgia paresthetica, etc.[8-11] Compression of the nerve leads to symptoms such as a tingling sensation and sometimes pain in sensory nerves and can result in numbness as the entrapment persists and the nerve becomes ischemic.[12] Aberrant action potentials of the strained nerve can be subject to central sensitization, thus inducing a chronic pain state.[13] The complex and likely variable anatomy of anterior cutaneous nerves suggests that an entrapment mechanism is possible in narrow compartments and fascial layers comprising the abdominal wall, although likely rather different from the manner Applegate proposed.[14] However, classic neuropathic features such as tingling, electrical, shooting of burning sensations are not the typical pain characteristics that patients refer to in ACNES.[15] Using the internationally accepted DN4-score for assessing neuropathic pain asking 10 questions (0, neuropathy unlikely; 10 point, very likely) about the nature of the patients pain, only ACNES patients who have somatosensory disturbances and experience 'pricking' with worsening of pain upon light touch have a borderline 4 out of 10 points.[16] Patients who only have a painful fingertip point with a positive Carnet´s sign would classify as 2-3 out of 10, which by definition excludes the presence of neuropathic pain. Nevertheless, the clinical picture surely fits pain in the distribution of the periphery of the intercostal nerve endings. This conclusion is underlined by the fact that in over 80% of patients typical somatosensory disturbances in a small (and not complete dermatome-like) area are present: hypoesthesia, hyperpathia, pinching and altered cool perception.

The most likely etiological explanation is that ACNES now comprises a heterogenous group of pathophysiological pain states. Some pain is due to purely mechanical mechanisms, others are the results of peripheral or central sensitization originating from perhaps a diseased viscus, a third category is a mix of both. Future studies should prospectively follow patients in subcategories based on etiology, DN4 score or presence of pseudo visceral complaints and should go into more detail regarding functional testing of the nerves. This approach might possibly lead to a distinction between "pseudo" ACNES and "true" ACNES: the first being significantly more complex to investigate, although there is extensive basic science behind viscerosomatic convergance occurring in visceral inflammatory conditions.[5]

Nevertheless, as long as there are no objective, instrumental measures to determine whether or not a patient has ACNES (be it "pseudo" or "true"), treatment results are needed to make a convincing point that the diagnostic criteria that are presented in this thesis are useful. The current large patient series was used to analyze the effects of injection therapy trials and factors predicting outcome after an anterior neurectomy. Success rates of surgical intervention are consistent with earlier research and are comparable with results of a neurolysis in carpal tunnel syndrome (75%) and meralgia paresthetica (78%).[17,18]

The overall short term beneficial effect of injections into the point of maximum pain is high, as has been described in previous articles and confirms it as the current gold standard diagnostic test, but the long term effects on pain relief are fairly poor.[19] In the long term, just a minority (<20%) benefits from injection therapy alone. For select subgroups, such as pediatric patients, success may be somewhat higher, but when it comes to improving treatment results this thesis indicates that the focus should be on local nerve destruction and spinal cord stimulation.

CPIP

CPIP is a prime example of neuropathic pain arising from nerve injury. Injury to a nerve fiber can lead to a process called Wallerian degeneration: the distal part of the axon degenerates.[20] Scar tissue surrounding the nerve stump can form into an end neuroma, which can become painful if it is exposed to compression.[21] A neurectomy in the case of inguinodynia supposedly works by relocation of the end-neuroma to an anatomical space where it's less susceptible to sheer stress and compression.[22]

The last chapters of this thesis describe patients who did not benefit from a neurectomy, perhaps because of central sensitization, perhaps due to other reasons. Spinal cord stimulation (SCS) may be an interesting option for patients with CPIP in general.[23,24] The preliminary results in 18 patients of the SMASHING trial randomizing SCS or standard conventional therapy suggest that SCS is superior in these complex, therapy resistant patients.

However, given the high rate of device-related and procedural adverse events, it is absolutely vital to optimize technical aspects and implanter skills in the field of DRG SCS. At present, the actual result of stimulation might be understated due to recurrence of pain during device-related complications such as lead dislocation, causing suboptimal effects. If these problems are solved, more patients will probably consider this therapy a viable option, and higher inclusion rates in trials will become more feasible.