Summary and conclusions

ETIOLOGY, EPIDEMIOLOGY AND TREATMENT OF ACNES

The main theory on the pathophysiology of ACNES has largely been shaped by one dedicated US family doctor, William Applegate.[38] He proposed an entrapment mechanism posterior of the rectus abdominis muscle, based on detailed figures of the trajectory of intercostal nerves in anatomy books.[39] it is rather unclear whether his pathophysiological explanation is as sound as it may seem. Moreover, his mechanistic hypothesis does not explain the entire symptom complex of all ACNES patients. Nevertheless, the impact of his theory on developing successful therapeutic strategies has been huge. Fundamental studies on the topography of intercostal nerves, however, are very scarce, and thus the 'real life', actual anatomy was just unveiled to surgeons performing an exploration and a neurectomy. **Chapter 2** provides a snapshot of the complex neuroanatomy of the abdominal wall and illustrates some visual and histological evidence of the alleged culprits of ACNES. Multiple unpredictable interconnections between intercostal nerves were observed at various levels of their travels from posterior to anterior portions of the abdominal wall. Performing a successful neurectomy might therefore be far more difficult than previously assumed. Moreover, a highly unpredictable neuro-anatomy is likely the main reason for failure after surgery.

The single center series of over 1100 ACNES patients described in **Chapter 3** would undoubtedly have been of much interest to dr. Applegate. Symptoms that were briefly mentioned in earlier case studies throughout history (e.g. Carnett's test), were indeed found to be present in >80% of patients who were suspected of having ACNES.[40] Almost half reported complete but temporary pain relief following an abdominal wall infiltration using lidocaine at their painful point, and one third reported >50% pain relief after several injections. Interestingly, the area that is mostly affected in ACNES patients is at McBurney's point. A typical ACNES patient is a young or middle-aged female with severe continuous right-sided lower abdominal pain that developed spontaneously without any evident cause strongly mimicking appendicitis. A subgroup (approximately 10%) presents with bilateral symptoms – practically always at a symmetrical level - or with several tender points along the trajectory of the intercostal nerve, which is suggestive for central sensitization with mirroring of pain perception of an initial localized neuropathic pain entity.

Chapter 4 and **5** show that corticosteroids have no added effect in peripheral nerve blocks in ACNES. 136 patients were randomized in two equal arms receiving three injections with either lidocaine *plus* corticosteroids, or lidocaine alone. No group differences in pain reduction were found. The number of successful responders, defined as >50% pain reduction on a Numeric Pain Rating Scale two weeks after the end of treatment, was not different between groups. Long term pain reduction after 6 weeks decreased equally in both groups to an approximately 20% success rate. **Chapter 6** shows a 38%

long term and therefore higher success rate (median follow-up 17 months) of injection therapy in children.

Chapter 7 identifies patient characteristics that predict a negative outcome after an anterior neurectomy in ACNES. Previous abdominal surgery, preoperative medication use, absent pain relief following a first diagnostic block and trigger points beyond the abdominal wall in the trajectory of the intercostal nerves (such as paravertebral or flank) were associated with a failure. However, a prognostic model that was created with these four factors had rather suboptimal discriminative value (AUC of 0.67). This finding suggests that other, unstudied factors are possibly of greater importance in determining therapy outcome. Nonetheless, this model can be used to counsel patients prior to invasive treatment. If even a second neurectomy fails to substantially reduce pain levels, **chapter 8** shows dorsal root ganglion (DRG) stimulation is a viable option in ACNES patients. In a small case series, 3 of 5 patients experienced >50% long term pain reduction. **Chapter 9** incorporates these treatment considerations in the new Dutch Pain Guidelines, established by the Nederlandse Vereniging voor Anesthesiologie, sectie Pijngeneeskunde (NVAsP).

DRG SPINAL CORD STIMULATION IN CHRONIC POST-SURGICAL INGUINAL PAIN (CPIP)

This part describes the study protocol (**chapter 10**) and preliminary results (**chapter 11**) of a multicenter randomized controlled study comparing DRG spinal cord stimulation (SCS) to conventional medical management (CMM). Patients with CPIP (>6 months) after either a laparoscopic or open hernia repair or Pfannenstiel incision with no or only a partial response to a neurectomy were randomized to either DRG SCS or CMM. The CMM group had the option to cross-over after 6 months. The study was powered to a total of 78 patients.

Fourteen patients reached the primary endpoint of 6 months follow-up in 2017 and their data were used for a per protocol analysis. Six of nine patients randomized to the DRG SCS group received a permanent Implantable Neurostimulation System. Three patients experienced a negative trial period indicating that the system did not result in pain relief and continued with prior pain medication regimens or other pain treatments. Six of nine patients in the CMM group eventually chose to cross-over after 6 months of follow-up and received a permanent INS. Reasons for not switching to the DRG SCS group were fear of complications or significant comorbidity. In the pooled group of 8 implanted patients, a 49% pain reduction (NRS 6.60±1.24 to 3.28±2.30) at 6 months of follow-up was detected, In contrast, a slight 13% increase in pain in n the CMM group was observed over this time period. A repeated measures ANOVA revealed a significant

group difference at 1, 3 and 6 months follow-up (p=0.001). Adverse events such as lead dislocation and lead breakage occurred in 9 patients with a total of 19 incidents. Secondary outcome measures such as quality of life and functionality also improved in the DRG SCS group compared to CMM, acknowledging the potential of this novel therapy for CPIP patients.

CONCLUSIONS OF THIS THESIS

1. The anatomy of intercostal nerves at the abdominal wall level is more complex than previously hypothesized.
2. The typical ACNES patient is a young or middle-aged female with severe continuous right-sided lower abdominal pain that developed spontaneously without any evident cause.
3. Corticosteroids have no added effect in peripheral nerve blocks/ injection therapy in ACNES.
4. The long term success rate of injection therapy in children is 38%.
5. Previous abdominal surgery, preoperative medication use, absent pain relief after first diagnostic block and trigger points beyond the abdominal wall in the trajectory of the intercostal nerves are associated with a failure after a neurectomy.
6. Dorsal root ganglion stimulation is a viable option for treating therapy resistant ACNES and CPIP patients.
7. Device-related adverse events in DRG therapy for CPIP are, unfortunately, common.

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