Factors predicting outcome after anterior neurectomy in patients with chronic abdominal pain due to anterior cutaneous nerve entrapment syndrome (ACNES)

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ABSTRACT

Background: Chronic abdominal pain due to the anterior cutaneous nerve entrapment syndrome (ACNES) may require surgery providing long term pain relief in up to 70% of operated patients. Factors predicting outcome following an anterior neurectomy are unknown. Aim of the study is to identify factors associated with treatment failure possibly allowing for optimizing patient counselling and selection.

Methods: Characteristics of ACNES patients unresponsive to nonsurgical therapies undergoing an anterior neurectomy in a tertiary referral center in the period 2011-2016 were analyzed. Treatment failure was defined as a <50% pain reduction using a numeric pain rating scale (NRS 0-10) approximately two months postoperatively. A prediction model based on a multivariate regression analysis was tested for its discriminative value.

Results: A total of 495 patients (78% female, median age 40 yrs, range 8-83) undergoing an anterior neurectomy were eligible for analysis. Pain medication use (OR 1.84, p=0.027, CI 1.07 – 3.17), previous abdominal surgery (OR 1.85, p=0.026, CI 1.08 – 3.18), the presence of paravertebral tender points at exits points of intercostal nerves (OR 2.58, p=0.003, CI 1.39 – 4.80) and failure to favorably respond to a diagnostic rectus sheath block (OR 3.74, p=0.000, CI 3.74 – 7.10*)* were identified as factors predicting surgical failure. However, a prediction model including these four factors had poor accuracy with an AUC of 0.64 (CI 0.58 – 0.70).

Conclusions: The present study identified risk factors associated with treatment failure that are useful in counseling ACNES patients prior to a surgical intervention.

BACKGROUND

Up to 30% of patients with chronic abdominal pain of unknown origin may suffer from an abdominal wall related syndrome, for example the anterior cutaneous nerve entrapment syndrome (ACNES).[1,2] Discomfort associated with ACNES is often mistakenly considered by physicians as visceral pain due to irritable bowel syndrome.[3] However, a detailed physical examination in an ACNES patient may identify distinct properties such as altered abdominal skin sensation, a positive Carnet's sign and a predictable fingertip point of maximum pain . [4,5] The abdominal pain is supposedly caused by entrapped sensory cutaneous terminal branches of abdominal intercostal nerves at the level of the abdominis rectus muscle.[6,7]

At the start of the 21st century, the diagnosis ACNES was considered controversial and was seldom listed in differential diagnostic considerations of abdominal pain entities. In the Netherlands however, there is now increasing recognition of this syndrome amongst general practioners and specialists. Treatment modalities such as injection therapy[8], pulsed radio frequency ablation (pRF)[9] or a neurectomy[10,11] of entrapped nerves were all, to a certain extent, found to be successful in selected patients. Early favorable experiences led to create a dedicated outpatient clinic for patients with abdominal wall and groin pain. An overwhelming response of referrals following media-attention and peer group lectures followed in suit. As a consequence, over 1500 ACNES patients were evaluated and treated at this center of expertise between 2003 and 2017.

Previous research in this extensive patient population included randomized controlled trials on the efficacy of local injection therapy and a surgical neurectomy, as well as alternative secondary approaches for non-responders.[10,11] However, surgical success is not always achieved. Considering a 70% long term surgical success rate, the identification of factors potentially predicting the efficacy of a neurectomy may aid in counseling these patients with often severe pain (NRS 7-8) prior to initiating any form of invasive surgery.[12] Aim of this prospective database study is to identify patient characteristics that are associated with treatment failure allowing for optimizing patient selection.

METHODS

Data sources

This study analyzed prospectively collected data of 1014 consecutive patients who were diagnosed and treated for ACNES at the SolviMáx Center of Excellence for Abdominal Wall and Groin Pain, Eindhoven, The Netherlands, between May 2011 and May 2016 as documented in standard hospital electronic patient files. Each patient is required per protocol to complete a number of standardized and center-specific questionnaires prior

to receiving an invitation for an outpatient evaluation. As a consequence, a complete and validated baseline information regarding a variety of parameters including duration, etiology, nature and disease burden is obtained. Numeric pain rating scores (NRS) and verbal pain rating scores (VRS) were used at follow-up visits to assess therapy success, occasionally converted by the treating specialist to percentage pain reduction following the therapy.

The center's step-up treatment protocol dictates a 6 week period of bi-weekly injection therapy in each new untreated ACNES patient followed by more invasive treatments such as pRF treatment. A neurectomy of the cutaneous intercostal nerves anterior to the rectus abdominis muscle is considered if all modalities fail. Details of this surgical procedure were published previously.[10] The effect of such a neurectomy is standardly assessed some 2 months after treatment during an outpatient follow-up visit.

Study design

This database study included all patients who were diagnosed with ACNES and who ultimately received an anterior neurectomy as a first step surgical procedure. A patient was considered to have ACNES if at least two of the three following characteristics were identified during the interview and physical examination:

- A history of abdominal complaints with one specific point of maximum pain
- Local somatosensory disturbances at this point of maximum pain, and/or a positive pinch test
- Positive Carnett's sign at the point of maximum pain[6]

Patients who underwent other types of surgery as a first procedure, such as a neurectomy posterior to the rectus abdominis muscle, were excluded. All patients signed informed consent forms allowing for the use of anonymized patient related outcome measures (PROM). Results of questionnaires data, patient history and physical examination were entered in the hospitals electronic files by treating specialists. Coding of these data into a study database was performed and monitored by two independent investigators.

Outcome variables

Surgical success was defined as a minimal 50% pain reduction on NRS scores compared to baseline values at 2 months follow-up after surgery as dictated by international pain literature standards and as previously published.[13,14] Long term success rates, encompassing recurrences after 2 months, were not investigated in this study.

Factors possibly related to outcome

Characteristics potentially influencing treatment success based on previous pain literature were BMI, age, gender, duration of symptoms, average pain scores and medication use.[15-18] Treating specialists (MS and RR) suggested that a number of ACNES specific fac-

tors such as onset mechanism, previous abdominal surgery, uni- or bilateral complaints, anatomical level of pain, previous treatments, effect of a diagnostic rectus sheath block and presence of intercostal or paravertebral tender points along the intercostal nerve's tract would all potentially be factors predicting failure or success. Comorbidities such as other pain syndromes or concurrent gastro-intestinal syndromes including IBS were also deemed relevant and tabulated.

Statistical methods

Data were analyzed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, US). The outcome measure was dichotomized by means of effectiveness (≥ or < 50% pain reduction, success or failure, respectively). Patient characteristics and clinical findings were dichomotized as well (except for age, duration of symptoms and NRS scores) and tested for confounding properties by univariate analysis. A variable was only tested for significance if at least 85% of the data were complete. Categorical demographic variables were compared using the x^2 test. Continuous data were analyzed using the independent t test or Mann-Whitney U test when appropriate.

Significant confounders ($p \leq 0.10$) were included as covariates in a multivariate logistic regression model as a means to determine a possible association between potential prognostic variables and outcome measures. The corresponding odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. A > 1.0 OR indicates a higher chance on failure, whereas a < 1.0 OR indicates a lower chance. A likelihood ratio backward (rather than a forward) stepwise regression method was utilized to limit the chance of suppressor effects and risk of a Type II error. The discriminative ability of the prediction model was assessed by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve and sensitivity and specificity of the model at multiple cut-off points. Statistical significance for the multivariate logistic binary regression was set at $p \leq 0.05$.

RESULTS

Patient selection

A total of 587 unique patients underwent a neurectomy for ACNES at the SolviMax center during the 5 year time period. Eighty-seven patients were excluded because a different neurectomy protocol was executed as the primary procedure, either because of an earlier neurectomy in a referring facility, or a posterior neurectomy (fig. 1). Follow-up data regarding the outcome variable was available in 99% (495/500) of patients. Subject characteristics are depicted in Table 1.

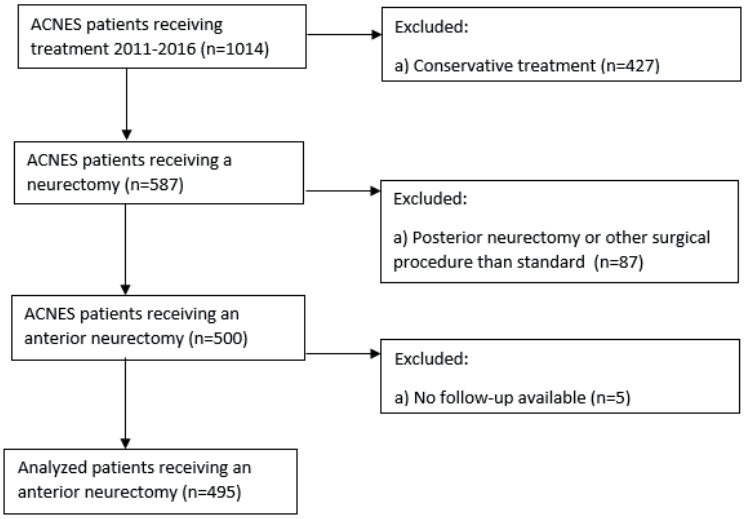

Fig 1. Patient selection

Table 1. Characteristics of ACNES patients undergoing an anterior neurectomy during a 5 years' time period in a tertiary referral center.

Patients		(n=495)
Age*		40 (8-83)
Sex ratio	M:F	1:4.5
Height (cm)**		169 (11) cm
Weight (kg)**		73 (17) kg
BMI (kg/m^2)**		25 (5)
Etiology (n)		
Spontaneous		56%
Recent abdominal surgery		30%
Accident/sport injury		5%
Pregnancy		3%
After a flu		3%
Other		3%
Duration of pain prior to diagnosis (months)*		26 (1- >120)
NRS normal**		6 (2)
NRS peak**		8 (2)
Previous conservative treatment elsewhere for ACNES		62%
Abdominal wall point of max. pain location (dermatome)		
Th7		2%
Th8		8%
Th9		11%
Th10		24%
Th11		37%
Th12		18%

Table 1. Characteristics of ACNES patients undergoing an anterior neurectomy during a 5 years' time period in a tertiary referral center. (*continued*)

Abdominal wall point of max. pain location (side)	
Right	57%
Left	27%
Bilateral	16%

NRS = Numeric Rating Scale; BMI = Body Mass Index. Data are presented as medians (*) with ranges or means (**) with standard deviations, as appropriate.

Estimates of effects in 495 ACNES patients

A total of 395 patients (79,8%) had a successful response (≥50% pain reduction) after a neurectomy. This percentage is consistent and similar to previously reported outcomes in various subgroups of this cohort.[9,19] A multivariable analysis including factors that were found by univariate analysis to negatively influence outcome demonstrated that medication use, previous abdominal surgery, the effect of a diagnostic rectus sheath block and the presence of paravertebral tender points along the nerve's tract were predictive (Table 2). Both the anatomical level of the point of maximum pain (abdominal quadrant) as well as old age were of relevance in the univariate analysis but appeared nonsignificant in the multivariate analysis and were thus removed from the final model.

These four factors formed a significant better model than a priori prediction for neurectomy failure but the model itself still had poor accuracy with an AUC of 0.64 (CI 0.58 – 0.70). An AUC of <0.70 is generally regarded as a 'poor' or 'failed' discriminative value (fig. 2). In other words, if the aim is that no therapy should be withheld from patients who would otherwise have had a successful neurectomy (high specificity) , the model is of limited value to predict therapy failure (low sensitivity). Interestingly, not a single patient in the present study cohort had all of these four risk factors.

Table 2. Factors associated with failure of an anterior neurectomy in ACNES patients

	B (SE) [p-value]	Odds	CI 95%
Constant	*-2,51(0.30)*		
Medication use	*0.61(0.28)[0.027]*	*1.84*	*1.07 – 3.17*
Previous surgery	*0.62(0.28)[0.026]*	*1.85*	*1.08 – 3.18*
Paravertebral triggerpts	*0.95(0.32)[0.003]*	*2.58*	*1.39 – 4.80*
Effect dx rectus block	*1.32(0.33)[0.000]*	*3.74*	*3.74 – 7.10*

R^2= 0.086 (Cox & Snell); 0.135 (Nagelkerke); Model X^2 34.14 P<0.001

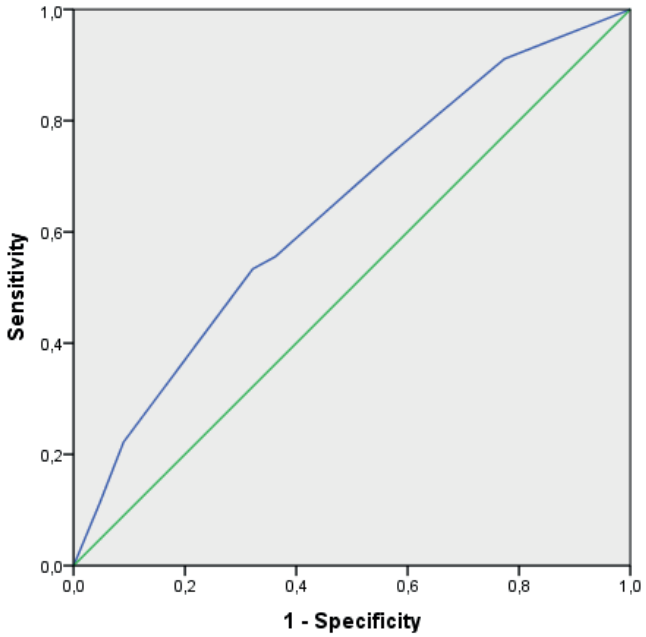

Fig. 2 ROC curve of a prediction model with factors associated with neurectomy failure.

DISCUSSION

The present study is the first to aim at identifying significant factors predicting failure of a neurectomy of the anterior twigs of the cutaneous branches of intercostal nerves in patients with ACNES. The a priori chance for failure is low, ranging from 20-30%, as an anterior neurectomy is an overall successful procedure that even leads to complete pain remission in a substantial subgroup of patients.[9] This, however, raises high expectations in a vulnerable patient group with severe pain. After a neurectomy failure, further surgical exploration by means of a posterior neurectomy can still benefit some 50% of the remaining patients, but beyond this procedure effective treatment options are scarce.[11]

Preoperative medication use, previous abdominal surgery, a negative response following a diagnostic rectus sheath block and the presence of paravertebral tender points were found to be associated with anterior neurectomy failure in this study. Unfortunately, a prediction model based on these parameters had a low discriminative ability and did not provide clear cut-off values dictating whether a neurectomy should be denied. Possible reasons for low predictive properties may be related to the influence of other, unstudied factors or to the strict definition of therapy failure that was used in the present study. Nevertheless, findings of this study will aid surgeons and pain specialists

in deciding to more adequately counsel patients for a neurectomy, particularly if they have multiple risk factors.

Interestingly, the present study also demonstrates that traditional predictors of poor pain therapy outcome such as female gender, duration of complaints, age or opioid use do not necessary apply in an ACNES population. [20] For instance, preoperative opioid use is a classic factor negatively influencing success of pain therapies.[21] In the present study, pain medication use was not restricted to opioids and often included regimens of amitriptyline and gabapentin, or just paracetamol. Rather than suggesting a mechanism of medication induced hyperalgesia as is observed specifically with opioid use, this factor might reflect a certain coping style that negatively influences the subjective experience of pain reduction opposed to patients who don´t use any medication and rely on lifestyle adjustments. [22] Addressing coping style in preoperative work-up should be an important part of counseling, but is unfortunately often neglected.

The present study also identified previous abdominal surgery as a factor associated with poor outcome after an anterior neurectomy. Earlier abdominal surgery, defined as either an open or a laparoscopic procedure in the 10 years previously, may have changed normal anatomy of the abdominal wall. Tissue in proximity to incisions or trocar entry points may have scarred, but the sheer inflation of the abdominal cavity during laparoscopic surgery could possibly also damage small cutaneous nerves by an excessive traction force. It is, however, remarkable that if surgery clearly is identified as the onset mechanism for ACNES by the patient, this doesn't negatively influence the outcome of a neurectomy, compared to the majority of patients who spontaneously develop symptoms without evident cause.

A third factor determining surgical failure is related to the patient's response to a diagnostic abdominal wall infiltration using an anesthetic agent. An inappropriate pain reduction after a diagnostic block may indicate central sensitization or spread, or a faulty administration. One may decide to repeat this block as it is our experience that a second effort may be successful, possibly guided by ultrasound. However, even unsuccessful rectus sheath blocks do not necessarily result in futile surgery. The value of this important risk factor must be discussed with each potential patient prior to embarking on surgery.

A fourth risk factor associated with a unsuccessful result after an anterior neurectomy is the presence of paravertebral tender points. This finding suggests a spread of abnormal stimulation over the entire sensory nerve trunk.[27] In essence, ACNES is an entity involving intercostal nerves, or portions thereof. One may speculate that the severity of the intercostal nerve dysfunction is reflected by the extension of the painful area. In other words, a subgroup of ACNES patients having pain in the abdominal, flank as well as back area (along all portions of the intercostal nerve) are more likely to suffer from a more severe form that may be refractory to an anterior neurectomy. It is advised

to standardly check for trigger points along the flank and back as their presence may be used in the counselling of preoperative patients. Conversely, paravertebral pulsed radio frequency treatment or dorsal root ganglion stimulation may possibly be more beneficial in these patients. [28]

Identifying risk factors associated with an anterior neurectomy fuels the discussion on the etiology of this intriguing syndrome. Although entrapped end twigs of intercostal nerves traversing the rectus muscles supposedly are the culprit in this peripheral neuropathy, anatomical findings show that the anterior ventral branches of intercostal nerves seem to travel rather freely over the muscles towards the skin.[22] Neuroma formation, a feared complication following neurectomies such as Morton's neuralgia, may potentially also be found in 'postsurgical' ACNES. However, neuroma formation is seldom demonstrated during ACNES surgery.[24] Histological hallmarks of entrapment such as perineural fibrosis or edema are also only incidentally encountered. These findings suggest that other than pure mechanistic pathways may be responsible for the pain in a large portion of patients. The role of segmental relations between intercostal nerves and viscera via splanchnic chains explaining pain in some patients is also unclear.[25-28]

In conclusion, the results of this study will prove valuable to surgeons and pain specialists that consider performing a neurectomy for ACNES but primarily find clinical application in counseling patients prior to surgical intervention that have one or multiple risk factors. There are no better treatment options up to date and clear harm – benefit considerations are lacking as post-dissection pain or other permanent complications are scarce. Thus, a neurectomy could always be explored. But the chance of increased risk of failure should be explicitly addressed.

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