

# Bilateral distribution of anterior cutaneous nerve entrapment syndrome (ACNES): are clinical features and outcomes comparable to unilateral ACNES?

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## ABSTRACT

**Background and objectives** Mirror-image pain may occur in the presence of a one-sided peripheral nerve lesion leading to a similar distribution of pain on the contralateral side of the body (“mirrored”). Anterior cutaneous nerve entrapment syndrome (ACNES) is a neuropathic pain syndrome due to entrapment of terminal branches of intercostal nerves T7–12 in the abdominal wall and sometimes presents bilaterally. This study aims to address specifics of bilateral ACNES and to determine potential differences in clinical presentation and treatment outcomes when compared with the unilateral form of ACNES.

**Methods** Electronic patient files and questionnaires of a case series of patients who were evaluated for chronic abdominal wall pain in a single center were analyzed using standard statistical methods.

**Results** Between June 1, 2011 and September 1, 2016, 1116 patients were diagnosed with ACNES, of which a total of 146 (13%) with bilateral ACNES were identified (female, n = 114, 78 %; median (range) age 36 (1181) years). Average NRS (Numeric Rating Scale; 0–10) scores were similar (median (range) NRS scores 6 (0–10) although peak NRS scores were significantly higher in the bilateral group (9 (5–10) vs 8 (2–10); p=0.02). After a median of 26 months (1–68), the proportion of patients with bilateral ACNES reporting treatment success was 61%.

**Conclusions** One in eight patients with ACNES has bilateral abdominal wall pain. Characteristics are similar to unilateral ACNES cases. Further studies aimed at underlying mechanisms in mirror image pain pathogenesis could provide a more targeted approach in the management of this neuropathic pain.

## INTRODUCTION

Chronic abdominal pain (CAP) is usually attributed to diseases of internal organs.<sup>1</sup> However, in up to 30% of patients with CAP, pain is found to originate from the abdominal wall rather than from a viscus.<sup>2</sup> CAP in these individuals often results from anterior cutaneous nerve entrapment syndrome (ACNES) although this diagnosis is frequently not considered.<sup>3</sup> Wrongfully attributing CAP to intra-abdominal disorders could lead to unnecessary consultations, testing, and even futile abdominal surgery.

Considering the neuroanatomy of the abdominal wall may facilitate the understanding of the pathology of ACNES. The abdominal wall is sensory innervated by anterior and lateral cutaneous

branches of anterior rami of the thoracic intercostal nerves (7th–12th).<sup>4</sup> It was theorized that anterior intercostal nerve branches at ventral portions of the abdomen are triggered by an unknown pathophysiological event leading to a local anterior abdominal pain syndrome in the area of the rectus abdominal muscle.<sup>4</sup> Specific ACNES characteristics include a small area (several square centimeters) of maximal pain, altered skin sensation covering this tender point, a positive Pinch test and a positive Carnett’s test (increased local tenderness by tensing the abdominal muscles).<sup>1</sup> Recent studies demonstrated that lateral and posterior cutaneous branches are also able to generate neuropathic flank and back pain syndromes mimicking ACNES.<sup>5,6</sup>

Unpublished data from our institution regarding a large cohort encompassing 1116 patients diagnosed with ACNES showed that 13% presented with a bilateral pain syndrome. It is our experience that bilateral cases most often have pain at an identical dermatome level: “mirrored” (eg, bilateral T10: right and left at umbilical level). It is thought that a complex underlying mechanism of “communicating” neural pathways may occasionally result in bilateral pain. Aim of our study is to report on specifics of this complex subtype of ACNES. Unique findings at physical examination, pathophysiologic mechanisms and treatment results of this subdivision of patients with ACNES are discussed.

## METHODS

### Setting

A cohort study was performed between November 2017 and February 2018 in the Department of General Surgery of Máxima Medical Centre (MMC), The Netherlands. This study analyzed data from consecutive patients who were referred for a potential abdominal wall pain or groin pain syndrome to the SolviMáx Center of Excellence for Abdominal Wall and Groin Pain, Eindhoven, between June 1, 2011 and September 1, 2016. All patients provided signed informed consent forms prior to an outpatient department intake allowing for the use of anonymized patient-related outcome measures. The ethics committee of our hospital judged that results of the present study were obtained as part of an evaluation and auditing process of patient response outcome measurement. This manuscript adheres to the applicable STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.



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## Patient assessment

The presence of typical characteristics of ACNES was standardly assessed during physical examination as previously described.<sup>7</sup> These assessments included sensory mapping of tactile and cool sensation by using a cotton swab and an alcohol-soaked gauze to detect somatosensory disturbances of the skin covering the point(s) of maximal pain, Carnett's test (increased local tenderness by tensing the abdominal muscles) and the Pinch test (disproportional increase of pain while manually pinching an abdominal skinfold containing skin and subcutaneous tissue).<sup>4,8</sup> Whenever the diagnosis of ACNES was then likely, a diagnostic injection with lidocaine was proposed. After informed consent was obtained, patients were placed supine on a stretcher. After skin disinfection, an injection of 2–5 mL 1% lidocaine just underneath the anterior fascia of the rectus abdominis muscle was administered using a 21 G 40 mm needle. Volume was based on patient's weight and/or subcutaneous thickness around the tender point. Needle tip placement was just beneath the fascia of the rectus abdominis muscle, ideally into or in close proximity to the tender point using a free hand technique, as previously published for ACNES.<sup>7</sup> The pain was subsequently measured on a numeric rating scale (NRS, 0 (no pain) to 10 (worst possible pain)) immediately before and some 10–15 min after this abdominal wall injection. If levels of (spontaneous) resting pain were considerably lower and success was attained (defined as a >50% pain reduction), characteristics of the diagnosis were again communicated, and the patient received a control appointment after 2–3 weeks. If the pain had recurred by then, the patient underwent an injection regimen of repeated (1–3) local tender point infiltrations using 2–5 mL of 1% lidocaine. If levels of pain after this regimen remained unacceptable, or if patients declined ongoing injection therapy, they were either referred to a pain clinic for alternative treatments (eg, medication, physical therapy, transcutaneous nerve stimulation, or pulsed radiofrequency therapy (PRF)), or received a surgical neurectomy procedure.<sup>7</sup> Treatment success was defined as >50% pain reduction on the NRS. Results of the neurectomy procedure are scored as total (both sides), as well as per side.

Findings in patients with ACNES presenting with a symmetrical bilateral pain syndrome were often as follows. A portion of patients reported pain as more diffuse rather than a small predictable localized area as observed in patients with unilateral ACNES. Moreover, the location of the pain usually projected in the abdomen's midline or around the umbilical area. Most patients found it difficult to exactly determine which side was most painful. Other patients reported that pain had started at one side and extended to the contralateral side after some time. The presence of such a "mirroring" effect was defined as exhibiting similar pain characteristics (eg, sensory abnormalities such as hypoesthesia or allodynia) at the side opposite to the initial painful side. Sporadically, we encountered a bilateral ACNES presentation occurring at different dermatome levels (ie, patients complaining of pain in dermatome T7 right and T10 left). This was entitled as two different ACNES tender points and not classified as mirror-image pain.

## Eligibility criteria participants

Inclusion criteria consisted of (1) a >3 month history of abdominal pain of unknown origin, (2) a constant area of abdominal pain, with a finger-tip point of maximum pain, located at the lateral borders of the rectus abdominis muscle at both sites of the abdomen, (3) localized somatosensory disturbances (such as hypoesthesia, hyperesthesia, and/or altered cool perception).

Exclusion criteria were: abdominal pain occurring at different dermatome levels (ie, not symmetrical, being sporadically encountered), cognitive impairment or surgical-scar related pain syndromes.

Patients with unilateral ACNES were included as controls.

## Data accrual

Characteristics of consecutive patients with an abdominal pain of unknown origin possibly having ACNES who presented to our outpatient clinic are standardly entered in the hospital's electronic patient file database. An electronic search using a diagnosis code exclusively assigned to abdominal wall-related pain syndromes was performed for identification of all patients with ACNES. Possible eligible patients with a bilateral presentation of ACNES were extracted from this database and entered in a separate database for further analysis. Data of symmetrical bilateral ACNES regarding patient's assessment at the first visit, as well as data regarding, age, gender, body mass index, diagnostic delay, etiology, NRS scores, events possibly provoking the pain, time of follow-up, date of being pain-free or possible recurrences, were entered in a separate database. Patient characteristics, findings on physical examination, and results of initiated treatment were compared between bilateral and unilateral cases. Coding of data was done and monitored by two independent investigators. All data were anonymized.

## Literature search strategy for bilateral ACNES

Available literature on ACNES was obtained by an electronic search strategy in various databases (PubMed, MEDLINE, and Embase) using the following keywords (alone or in various combinations): ACNES, chronic abdominal wall pain, chronic abdominal pain. The search strategy included studies up to December 31, 2017. Selection was based on the abstract contents whereas reference lists were screened to ensure no relevant papers were missed. Studies were eligible if they were written in English, had full text available, included detailed information on patient characteristics and specifically reported bilateral cases and were published by groups other than our institution. Data that were extracted from papers included total number of patients, number of patients with a bilateral presentation of ACNES, gender ratio, age, and study design.

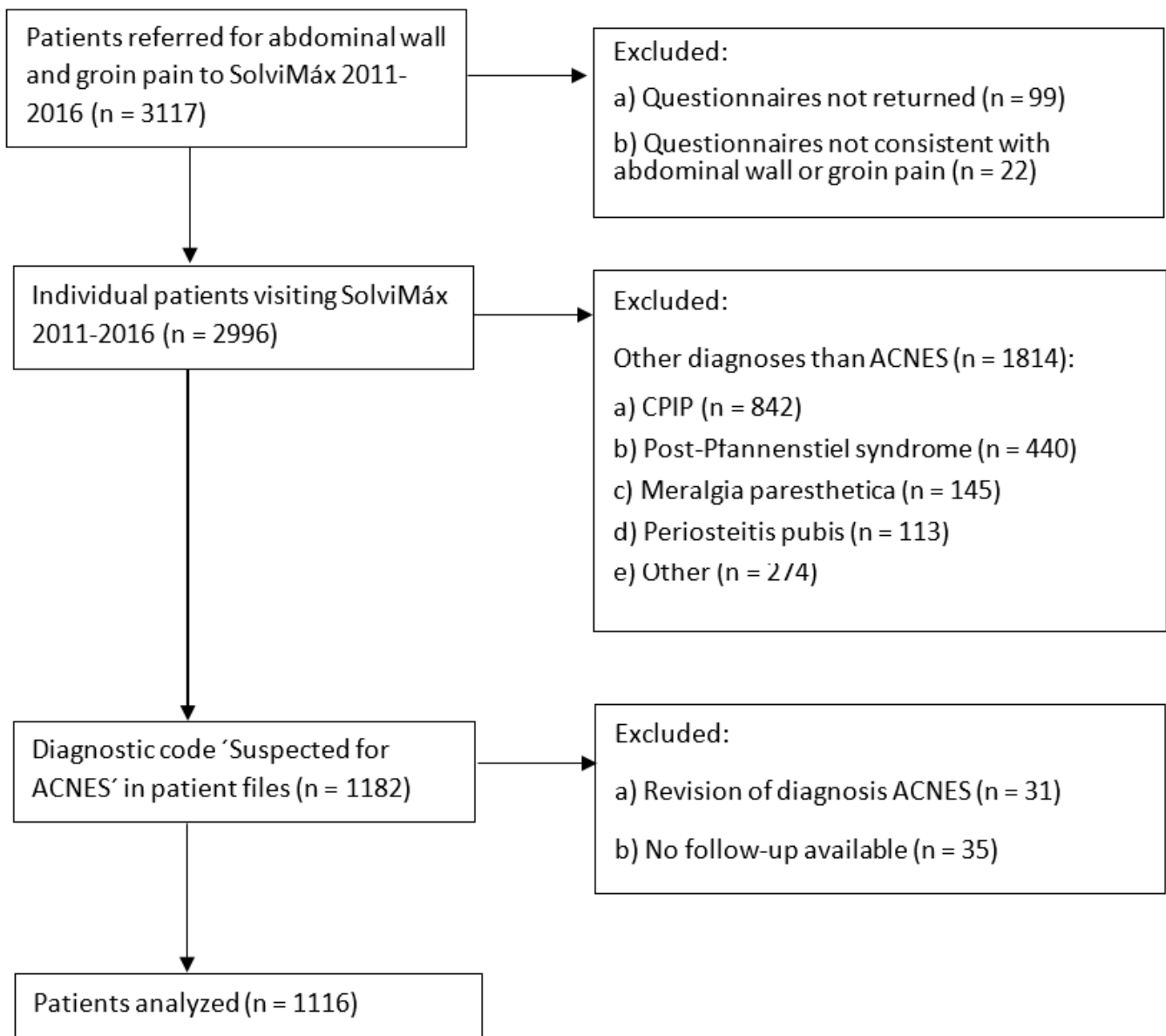
## Statistics

Determinants were analyzed if >85% data was complete using the Statistical Package for the Social Sciences (SPSS, IBM, New York, USA) V.21 for Windows. No date imputing was performed. Categorical variables were described as frequencies. Results for continuous variables were expressed as mean (SD) or as median (range) for variables following normal and non-normal distributions, respectively. Statistical testing for non-normally distributed variables used the Mann-Whitney test, and for categorical values the  $\chi^2$  test.  $P < 0.05$  was considered significant.

## RESULTS

### Patient selection

Over 3000 patients were referred to our outpatient clinic between 2011 and 2016 (figure 1), and 2996 were evaluated for a possible abdominal wall or groin pain syndrome. A total of 1182 patients were suspected of having ACNES whereas 1814 were excluded for reasons as depicted in figure 1. Therefore, the present study is based on 1116 patients diagnosed with ACNES. In this group, 970 patients (87%) presented with unilateral ACNES and 146 patients (13%) had a bilateral ACNES. However, in 4 of these



**Figure 1** Flowchart of patients with ACNES. ACNES, anterior cutaneous nerve entrapment syndrome; CPIP, chronic postherniorrhaphy inguinal pain.

146 patients dermatome levels which included the tender points were not symmetrically distributed and therefore excluded for further analysis.

### Subject characteristics

Demographics are depicted in [table 1](#). Characteristics regarding BMI, length, weight, duration of symptoms and etiology were comparable between the two groups. However, bilateral patients (n=142) were 8 years younger (bilateral: median age 36 (1–81) years vs unilateral n=970: 44 (7–81) years; p=0.02). Interestingly, in patients with unilateral ACNES, two age peaks were observed at 16 years and 40 years, while age was distributed more equally in patients with bilateral ACNES ([figure 2](#)). Average NRS scores were similar although peak NRS scores were significantly higher in the bilateral group (median 9 (5–10) vs 8 (2–10); p=0.02).

Findings on physical examination are shown in [table 2](#). Patients with bilateral ACNES presented with similar signs and symptoms on physical examination, although on both sides of

the anterior abdominal wall. As also reported for unilateral ACNES, the majority of bilateral cases (approximately 3 of 4) presented in the lower dermatomes T10–12. A positive Pinch test *and* a positive Carnett's test was observed in 82% and 84% of patients with bilateral ACNES, respectively (vs unilateral, 81% and 87%, respectively).

Specifics on onset of pain symptoms in bilateral ACNES were obtained from 138/142 (97%) patients. There was a right-sided preponderance as initial starting side of complaints (right-sided n=44 vs left-sided n=31); however, the majority of patients (63/142 (44%); p=0.004) reported that pain symptoms started on both sides simultaneously. Remarkably, almost one-third of these patients (19/63 (30%)) reported that their pain originated in the midline and spread toward left *and* right.

### Treatment results of symmetrical bilateral cases (n=142)

Median follow-up of the bilateral ACNES study population was 8 (1–68) months. Interventions are depicted in [figure 3](#). A total of 124 patients underwent injection therapy or/and PRF, with

**Table 1** Demographics of patients with ACNES presenting with a bilateral or unilateral pain syndrome

	Bilateral (n=142)	Unilateral (n=970)	P value
Age	36 (11–81)	44 (7–81)	0.02
Gender, M:F, (%)	32 (23):110 (77)	207 (21):763 (79)	0.75
Height, cm	170±8	169±10	0.84
Weight, kg	72±16	73±18	0.52
BMI, kg/m <sup>2</sup>	25±5	26±6	0.48
Diagnostic delay, months	23 (1-624)	18 (1-528)	0.67
Etiology, %			
Spontaneous	53%	60%	
Previous abdominal surgery	32%	27%	
Accident/sport injury	5%	5%	
Pregnancy	3%	3%	
After a influenza	3%	3%	
Other	4%	2%	
NRS normal (NRS, 0–10), (range)	6 (0–10)	6 (0–10)	0.24
NRS peak (NRS, 0–10), (range)	9 (5–10)	8 (2–10)	0.02

Data are presented as medians (ranges) or means (±SD), as appropriate. P value of <0.05 was considered significant.

ACNES, anterior cutaneous nerve entrapment syndrome; BMI, body mass index; NRS, Numeric Rating Scale.

28/124 (23%) patients experiencing >50% pain reduction. Eventually, 98/142 (69%) patients received a surgical intervention consisting of anterior *and* secondary posterior neurectomy when results of anterior neurectomy were insufficient.

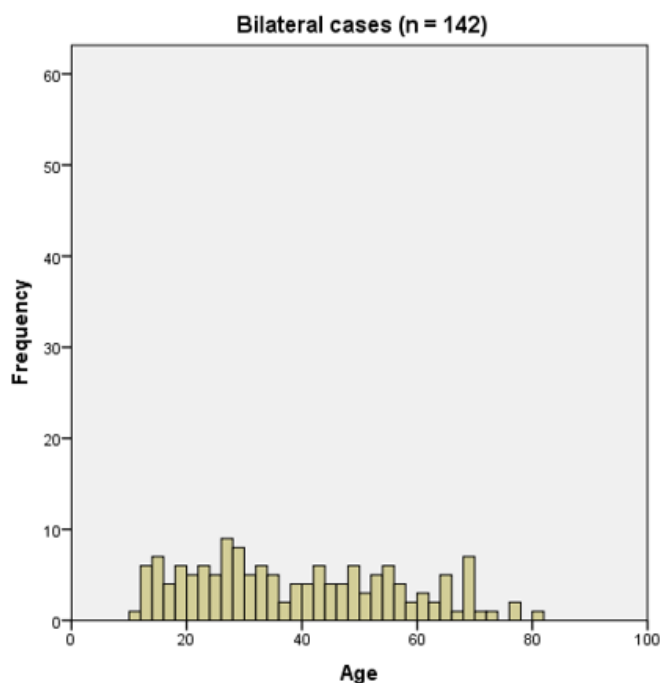
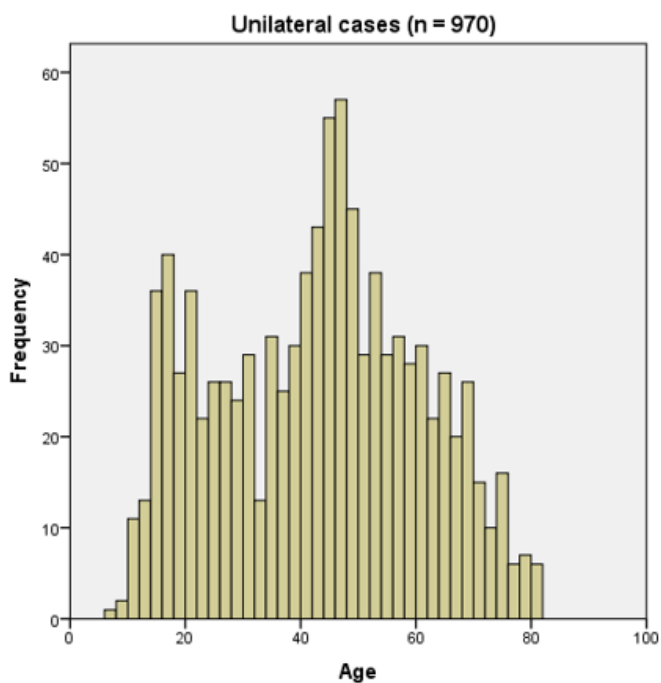
After surgical intervention, complete bilateral success was attained in more than half of the patients (53/98 (54%)) with median (range) follow-up time of 13 (2–68) months. An additional 6/98 (6%) patients had >50% pain reduction at either right (n=5) or left side (n=1).

**Table 2** Findings in patients with ACNES presenting with a bilateral or unilateral pain syndrome

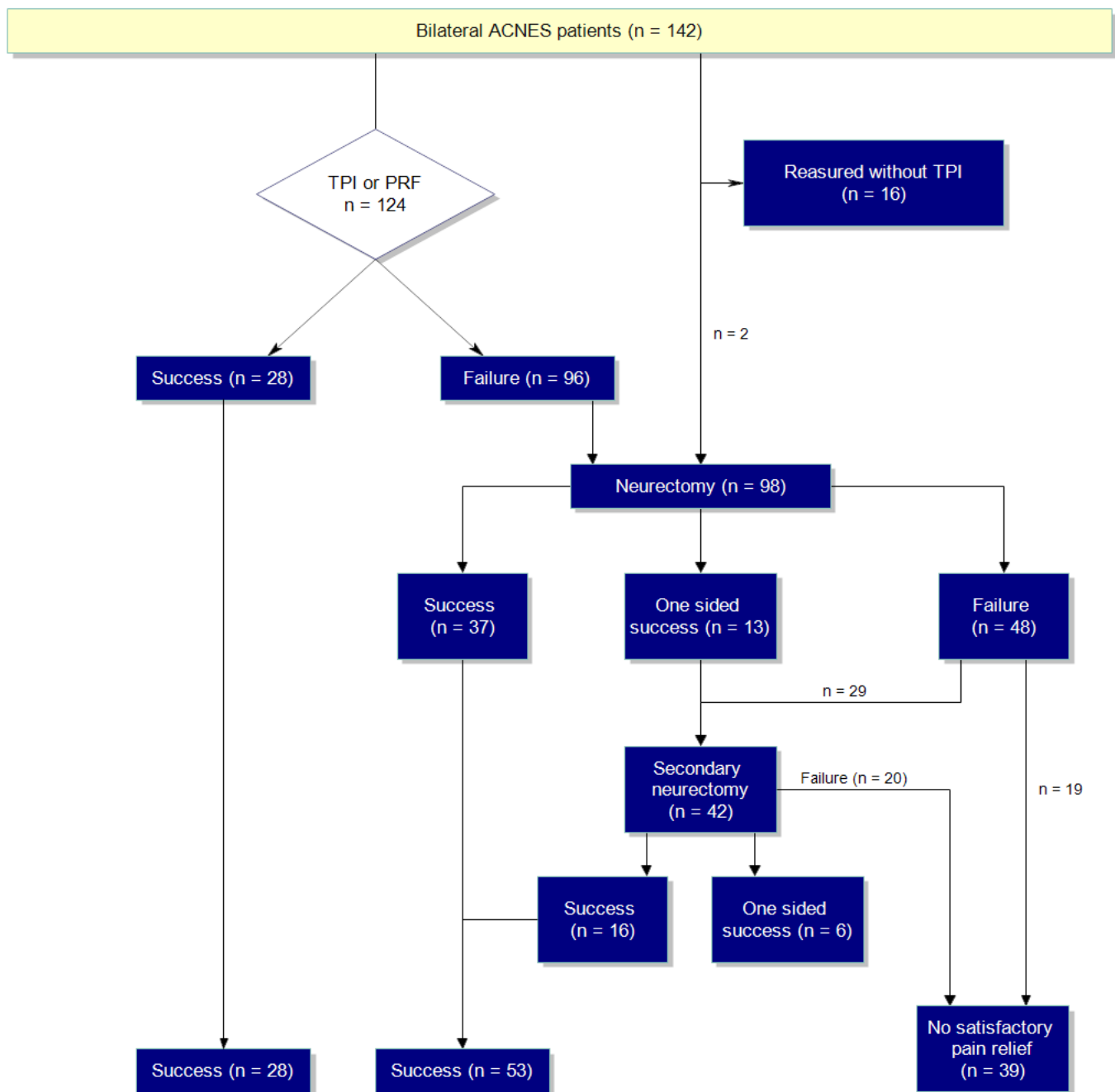
	Bilateral (n=142)	Unilateral (n=970)	P value
Abdominal wall dermatome of max. pain location			–
T7	3%	2%	
T8	10%	9%	
T9	15%	13%	
T10 (level of umbilicus)	29%	28%	
T11	27%	34%	
T12	16%	14%	
Abdominal wall side of max. pain location			–
Right	–	65%	
Left	–	35%	
Presence of local somatosensory disturbances around point of max. pain	71%	74%	0.59
Hypoesthesia	47%	49%	
Hyperesthesia	19%	20%	
Allodynia	5%	5%	
Positive Pinch test	82%	81%	0.44
Positive Carnett's test	84%	87%	0.56
Presence of intercostal painful points	18%	16%	0.66
Presence of paravertebral painful points	15%	15%	0.98
Reaction modified tender point injection after 15 min			
Pain-free	36%	38%	0.49
≥50% pain reduction	37%	34%	0.34
≤50% pain reduction	27%	28%	0.80

Data are presented as percentages of the entire case series.

ACNES, anterior cutaneous nerve entrapment syndrome; T, thoracic dermatomal level.



**Figure 2** Age of onset in patients with unilateral and bilateral ACNES. In unilateral cases (left), two peaks were present at around 16 and 40 years. In bilateral cases (right), patient's age was distributed more equally. ACNES, anterior cutaneous nerve entrapment syndrome.



**Figure 3** Flowchart of 142 patients with symmetrical bilateral ACNES showing consecutive steps in the diagnosis and treatment protocol. TPI and PRF indicate tender point infiltration and pulsed radiofrequency therapy, respectively. ACNES, anterior cutaneous nerve entrapment syndrome.

At the final follow-up visit, 87/142 (61%) of the bilateral ACNES cases reported a successful treatment result after either conservative measures such as injections, PRF or medication, or surgical intervention.

#### Literature search

The search strategy identified 115 papers on PubMed and 12 papers using Embase of which a total of 17 were considered eligible. Four studies were excluded since information on the exact pain location was absent.<sup>9-12</sup> Table 3 summarizes the remaining 13 studies encompassing a total of 613 patients with ACNES (largest cohort included 269 patients). Most reports were case series (n=9). A total of 62 (10.1%) bilateral cases of ACNES were identified from these reports. Numbers on the

prevalence of bilateral ACNES in literature correlate well with the observed cases in our study population, which was 13%.

#### DISCUSSION

The ACNES is a diagnostic struggle for various physicians ranging from surgeons, neurologists, gastroenterologists, pain specialists to general practitioners. As a result, ACNES is still often neglected as a possible cause of abdominal pain and discomfort and is considered a frequently overlooked diagnosis.<sup>3</sup> The diagnosis itself relies entirely on undertaking a thorough medical history combined with searching for sensitive clues at physical examination (circumscribed pain localization, positive Pinch test, Carnett's test and abnormal sensory mapping). Conversely, imaging and laboratory evaluations are

**Table 3** Authors, other than from our own institute, reporting on bilateral cases in patients with ACNES

Study	Country	No. of patients	No. of bilateral cases (%)	M:F ratio*	Age*	Study design
Applegate 1972 <sup>30</sup>	USA	62	5 (8)	14:48	NS	Case series
Baciarello 2017 <sup>31</sup>	Italy	5	1 (20)	4:1	65 (34–67)	Case series
Bairdain 2015 <sup>32</sup>	USA	9	2 (22)	2:7	14 (10–19)	Case series
Batistaki 2013 <sup>33</sup>	Greece	1	1 (100)	n/a	37	Case report
Birthi 2013 <sup>34</sup>	USA	1	1 (100)	n/a	33	Case report
Gallegos 1989 <sup>35</sup>	UK	26	3 (12)	5:21	41 (19–70)	Case series
Greenbaum 1994 <sup>36</sup>	USA	56	5 (9)	16:40	47 (16–85)	Case series
Imajo 2016 <sup>37</sup>	Japan	1	1 (100)	n/a	56	Case report
Kuan 2006 <sup>38</sup>	Taiwan	140	5 (4)	1:139	30 (20–52)	Case series
Shute 1984 <sup>39</sup>	Canada	269	36 (13)	NS	NS	Case series
Skinner 2007 <sup>40</sup>	Australia	7	1 (14)	1:6	13 (11–16)	Case series
Stirler 2016 <sup>41</sup>	Netherlands	30	1 (3)	10:20	45 (18–72)	Cohort retrospective
Towfigh 2013 <sup>42</sup>	USA	11	1 (9)	4:7	41 (15–64)	Retrospective case series
Total (n=13)		613	62 (10)			

Data are presented as median (range), unless mentioned otherwise.

\*Based on total study population.

ACNES, anterior cutaneous nerve entrapment syndrome; N/A, not applicable; NS, not specified.

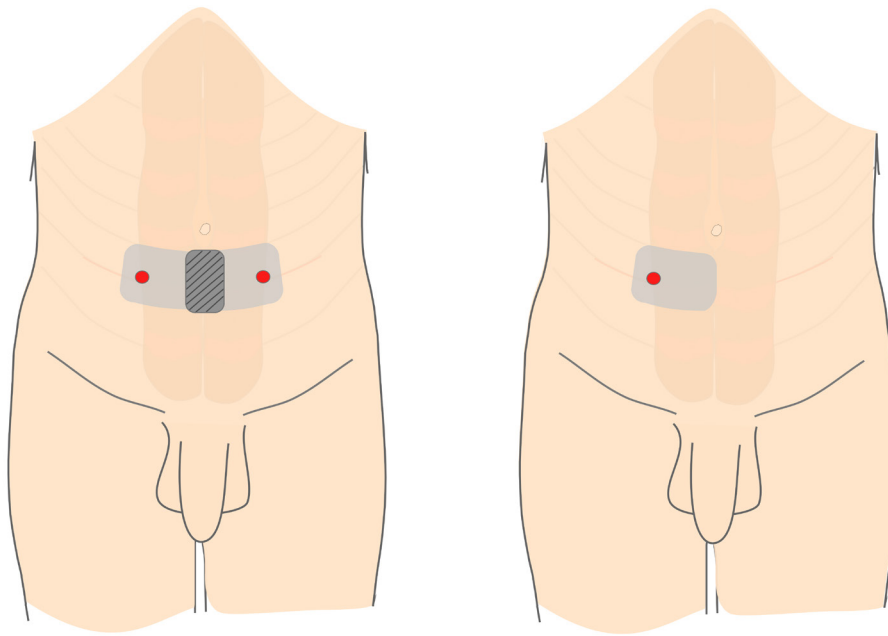
often noncontributing.<sup>7</sup> More complex subtypes of ACNES such as the bilateral variant likely are even harder to diagnose, thus lengthening an already substantial diagnostic delay. The present study is the first to report on a large series of bilateral ACNES cases and aims to contribute to the awareness of this difficult variant. Moreover, the present data show that a bilateral variant is practically always (97%) observed in a symmetrical (mirrored) distribution. Conversely, only 3% of patients presented with an asymmetrical bilateral ACNES, that is, a condition we consider as a coincidence of two concurrent unilateral cases.

Unilateral ACNES presents itself more frequently on the right side in a 4:1 ratio.<sup>7</sup> In more than half of the bilateral ACNES presentations (54% (75/138)), the onset was initially located at one side, either right or left, but also with a preponderance for right (60% vs 40%). In a substantial portion of patients, however, pain shifted over time toward the contralateral side leading to identical sensory changes as observed at the starting side of symptoms. This peculiar phenomenon is known as mirror image sensory dysfunction (MISD).<sup>13</sup> The phenomenon has been documented after surgery,<sup>14</sup> nerve injury,<sup>15</sup> in complex regional pain syndrome (CRPS) type,<sup>16</sup> and in rheumatoid arthritis.<sup>17</sup> Following unilateral nerve injury, contralateral sensory dysfunction, defined as neuropathic pain characteristics such as allodynia and hyperalgesia, may occur in selected patients.<sup>18,19</sup> It has been suggested that these MISD-responses to an injury are qualitatively similar but smaller in magnitude and have a briefer time course compared with responses at the injury site.<sup>20</sup> However, tissue injury is not required to invoke MISD as observed in healthy individuals subjected to low-intensity stimuli.<sup>21</sup> Therefore, awareness of this phenomenon could aid physicians in understanding and recognizing future patients with bilateral ACNES.

The origin of this bilateral distribution of pain and sensory dysfunction may either reside in the peripheral nervous system, the central nervous system or both. Several explanations may be forwarded. First, the medial branch of the anterior intercostal nerve may cross the midline, innervating the contralateral homologous paramedian skin area (figure 4). This would seem logical since a sharp demarcation border between different unilateral nerve innervation territories at least in the lower abdominal wall is absent.<sup>13</sup> Anatomical evidence for cutaneous

nerves of the anterior abdominal wall crossing the midline has been presented.<sup>22</sup> An explanation of the bilateral projection of pain and the distribution of the sensory dysfunction thus may reside in the peripheral nervous system. Second, the observed bilateral symptoms and sensory changes could be attributed to MISD.<sup>22</sup> Pursuing a physiological aspect, the nervous system exhibits a high degree of symmetry, which necessitates powerful transmedian communication systems to integrate and orchestrate the organism's homeostatic and behavioral mechanisms.<sup>20,23</sup> The exact underlying mechanisms of the transmedian communication, that is, "cross-talk" in MISD is unclear but seems to rely on combined cellular and humoral events. A contralateral response might be induced by a glial cell inflammatory response with subsequent release of cytokines leading to activation of central neural nociceptive pathways.<sup>24</sup> However, one study showed a peripheral pathway where unilateral nerve injury led to production of tumor necrosis factor alpha (TNF- $\alpha$ ) in the dorsal root ganglion (DRG) on the affected side.<sup>25</sup> It was hypothesized that TNF- $\alpha$  may diffuse via cerebrospinal fluid toward the contralateral DRG. TNF- $\alpha$  subsequently activates satellite glia to produce nerve growth factor leading to long-lasting mechanical hypersensitivity leading to mirroring of pain.<sup>25</sup> While there is thus evidence supporting both mechanisms, further studying of this rare phenomenon is warranted to uncover transmedian signaling mechanisms as well to improve our understanding of how brain activity "connects" both sides of the body.

Neuropathic signs and symptoms may be suspected during extensive history taking using specific questionnaires suggesting neuropathic pain such as DN4, or following simple tests during physical examination.<sup>26,27</sup> In ACNES, a meticulous physical examination may reveal a circumscribed pain localization, a positive Pinch test, a positive Carnett's test and/or sensory dysfunction such as hypoesthesia or hyperesthesia or allodynia.<sup>7</sup> A remarkable observation was that a proportion of patients reported that the experienced pain was most intense in the midline, presenting with corresponding sensory disturbances on both sides. This is practically always accompanied by other ACNES characteristics such as a positive Carnett's test and the Pinch test being symmetrically present on both sides of the abdomen. The above highlighted anatomy with midline crossing nerves may explain why the maximum pain is often felt in the very midline. We



**Figure 4** Distribution of sensory disturbances in patients with bilateral ACNES (left). Light gray area on the right and left shows distribution of sensory disturbances that can be found by sensory mapping, with a point of maximal pain (red dot). The hatched gray area at the midline shows the most painful area experience by the patient with overlap of sensory disturbances from left to right, crossing the midline. On the right side, distribution of sensory disturbances in patients with unilateral ACNES is shown. ACNES, anterior cutaneous nerve entrapment syndrome.

have also evaluated a number of patients with such a symmetrical bilateral pain syndrome at the umbilical level (T10) who were referred following an unsuccessful umbilical hernia repair elsewhere. Moreover, it may very well be that an initial neglect for the contralateral side could lead to this specific type of pain being overlooked, as is observed in ACNES in general.<sup>3</sup> Therefore, a physician should be aware of these bilateral presentations by frequently repeating ACNES-tests on the contralateral side.<sup>7</sup>

Apart from a more complex diagnostic pathway, an adequate treatment plan for bilateral ACNES is possibly even more challenging. Studies in type I CRPS demonstrated that recurrences in patients with bilateral presentations occur more frequently.<sup>16</sup> In this series of 1116 patients with ACNES, 98 of 142 (69%) bilateral ACNES cases proceeded to undergo a neurectomy. In the unilateral group (n=970), this number was 591/970 (61%). This difference is possibly due to the fact that unilateral patients respond slightly better to conservative treatment measures compared with bilateral ACNES cases. Our results also found a lower total success rate after bilateral anterior neurectomy (approximately 50%) compared with existing numbers on unilateral ACNES (70%).<sup>7</sup> Some patients reported that surgical intervention cured one side adequately, but did not lead to a successful result on the contralateral side. However, these seemingly inferior success rates have to be judged in the right context. When assuming that bilateral ACNES in fact are two independent ACNES entities, the a priori success rate after bilateral neurectomy is as low as 50%, as this can be estimated to be  $(0.7 * 0.7) * 100 \approx 50\%$ . This theoretical number correlates well with the observed success rate in the present study (some 54%). These considerations are important in counseling a patient prior to operation. Nevertheless, our experience is that bilateral ACNES is associated with lower complete success rates regularly requiring additional interventions.

We are aware of the limitations of the present study. An important limitation is the neglect of studying potential

abnormalities in central pain processing in this subpopulation. Quantitative Sensory Testing (QST) is a validated and commonly used tool for evaluating central nociceptive processing.<sup>28</sup> Treatment modalities that are directed at the nociceptive source (ie, the pain generator) can be expected to be less efficacious in the presence of central sensitization.<sup>29</sup> Since no QST tests were used in this large cohort, this effect remains unclear. Last, the diagnosis of ACNES in this cohort was neither established by objective tests such as laser evoked potentials, or nerve biopsies, nor by specific questionnaires suggesting neuropathic pain, including DN4, LANSS, or PainDETECT.<sup>26,27</sup> However, we hypothesize that the presently used tests during physical examination have sufficient diagnostic sensitivity.

In conclusion, this is the first large study reporting on the characteristics of patients with a bilateral ACNES. It is thought that this variant represents an example of MISD. This study adds to the existing knowledge helping physicians to adequately recognize and treat this complex subpopulation of patients with ACNES. Further fundamental research is needed to fully understand its complex underlying mechanisms.

**Contributors** RCM acquired and analyzed the used data and drafted the manuscript. MUW participated in analyzing used data and critically revised the manuscript. MRMS and RMHR participated in the design of the study and critically revised the manuscript. All authors discussed the results and commented on the manuscript.

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