PAIN® 154 (2013) 2877–2887

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Pain in chemotherapy-induced neuropathy – More than neuropathic?

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 17 March 2013
Received in revised form 16 July 2013
Accepted 26 August 2013

Keywords:
Chemotherapy
Polyneuropathy
Quantitative sensory testing
Musculoskeletal pain
Neuropathic pain
Pain drawings
Mixed pain

ABSTRACT

Chemotherapy-induced neuropathy (CIN) is an adverse effect of chemotherapy. Pain in CIN might comprise neuropathic and nonneuropathic (ie, musculoskeletal) pain components, which might be characterized by pain patterns, electrophysiology, and somatosensory profiling. Included were 146 patients (100 female, 46 male; aged 56 ± 0.8 years) with CIN arising from different chemotherapy regimens. Patients were characterized clinically through nerve conduction studies (NCS) and quantitative sensory testing (QST). Questionnaires for pain (McGill) and anxiety/depression (Hospital Anxiety and Depression Scale) were supplied. Patients were followed-up after 17 days. Large- (61%) and mixed- (35%) fibre neuropathies were more frequent than small-fibre neuropathy (1.4%). The 5 major chemotherapeutic regimens impacted differently on large- but not on small-fibre function and did not predict painfulness. Chronic pain associated with CIN was reported in 41.7%. Painless and painful CIN did not differ in QST profiles or electrophysiological findings, but different somatosensory patterns were found in CIN subgroups (pain at rest [RestP], n = 25; movement-associated pain [MovP], n = 15; both pain characteristics [MovP+RestP], n = 21; or no pain [NonP], n = 85): small-fibre function (cold-detection threshold, CDT: z score: −1.46 ± 0.21, $P < 0.01$) was most impaired in RestP; mechanical hyperalgesia was exclusively found in MovP (z score: +0.81 ± 0.30, $P < 0.05$). "Anxiety" discriminated between painful and painless CIN; "CDT" and "anxiety" discriminated between patients with ongoing (RestP) and movement-associated pain (MovP) or pain components (MovP+RestP). The detrimental effect of chemotherapy on large fibres failed to differentiate painful from painless CIN. Patients stratified for musculoskeletal or neuropathic pain, however, differed in psychological and somatosensory parameters. This stratification might allow for the application of a more specific therapy.

1. Introduction

Antineoplastic chemotherapy is an important cornerstone in the treatment of malignant tumours and has contributed to increased survival rates in cancer. However, chemotherapy-induced neuropathy (CIN) is a frequent cause for reduced quality of life that can lead to the discontinuation of treatment [13]. To date, no preventive therapeutic approaches have been available [2], so treatment strategies focus on symptom alleviation such as pain relief [13].

The damage of the afferent peripheral nerves in CIN implies that pain is predominantly of neuropathic origin [56]. Neuropathic pain presents with a variety of symptoms [44,51]. Recent approaches have tried to cluster patients according to their symptoms and signs to allow a more stratified mechanism-based therapy [5,8,44,46,51]. However, beyond neuropathic pain, nonneuropathic pain components might also be relevant: neuropathy leads to impaired sensory and motor function and nonphysiological movement patterns, resulting in biomechanical stress and musculoskeletal pain [17,41]. As musculoskeletal pain has been shown to mimic features of neuropathic pain (eg, pain referral [14,35]), inappropriate treatment (eg, antineuropathic treatment instead of physiotherapy) may occur. There may even be a combination of both pains – neuropathic and nonneuropathic, known as mixed pain [20,24,40].

Since these diagnostic problems are of paramount importance for treatment, the aim of this exploratory study was to find symptom patterns that might be indicative of neuropathic or musculoskeletal pain, or both.

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0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2013.08.028

2. Methods

2.1. Patients

Between 2006 and 2008, 378 of 763 consecutive patients from an oncological rehabilitation centre were identified with clinical symptoms suggestive of polyneuropathy (see Supplementary materials).

Of these, 175 patients agreed to participate in this explorative diagnostic study. All patients had undergone antineoplastic chemotherapy with complete or partial remission. No further chemotherapy was scheduled for the following 6 months. All patients reported that their neurologic symptoms had developed during chemotherapy. Patients with a history of diseases for preexisting neuropathy were excluded (see legend of Fig. 1). In total, 29 patients were rejected (Fig. 1). Final data analysis comprised 146 patients (F: 100; M: 46, aged 56 ± 0.8 years).

The mean latency from chemotherapy to study entry was 5.4 ± 0.6 months (Table 1). Only a small minority of patients (6 of 146) took pain medication on a regular basis (2 patients pregabalin and 4 patients gabapentin), which was not altered during the study. The study was approved by the Rhineland Palatinate Medical Association Ethical Committee and patients gave their written informed consent.

2.2. Clinical stratification

On their first visit, biographic, clinical, and therapeutic data were assessed in a structured interview and patients were assigned to 1 of the 4 subgroups, depending on their reporting:

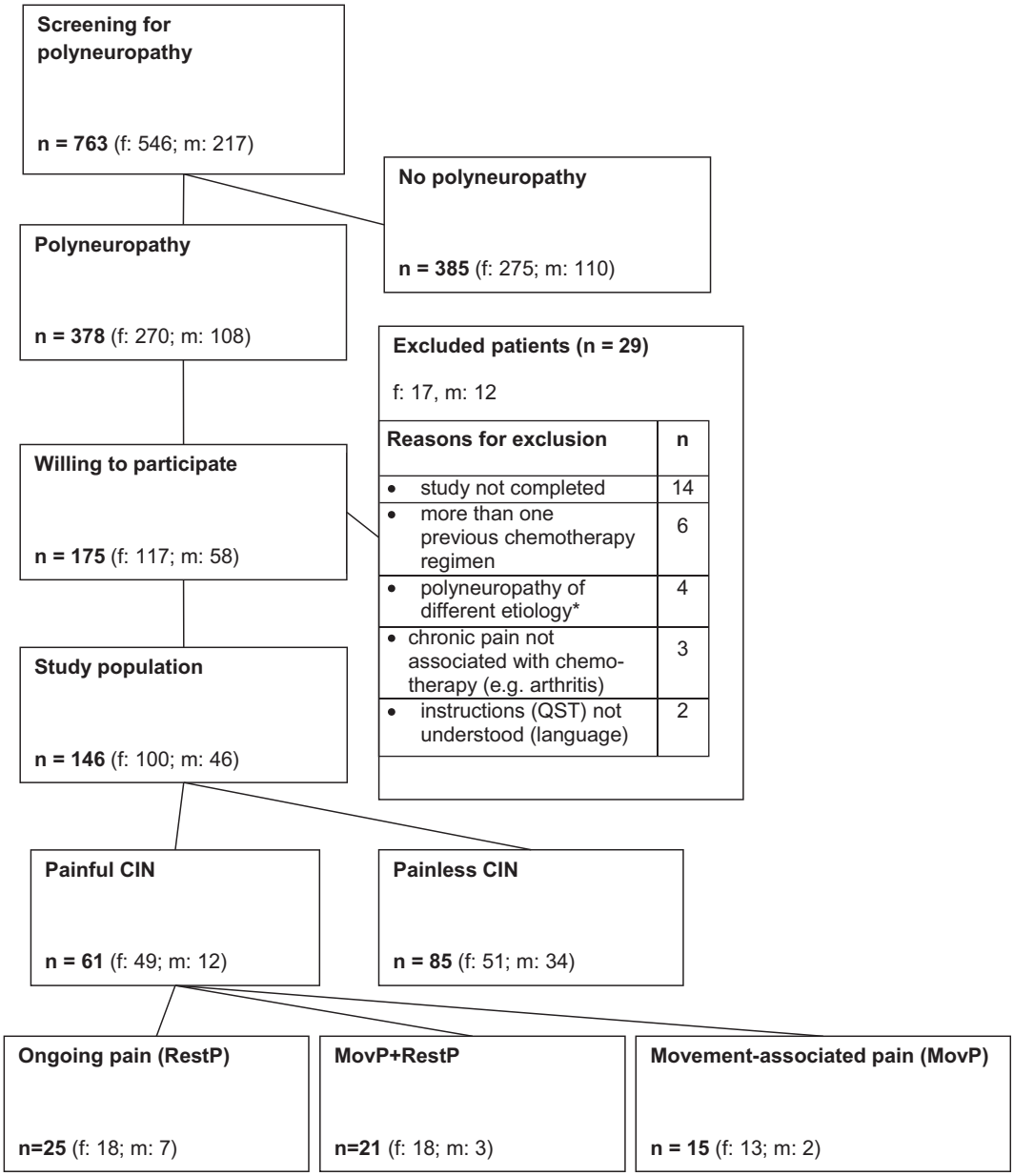

Fig. 1. Flowchart of patient stratification. Patients with preexisting polyneuropathy or medical history suggesting preexisting polyneuropathy (eg, due to diabetes; side effects of medication other than chemotherapy, eg, isoniazid or furantoin; alcohol abuse; hereditary polyneuropathy; malresorption; hypovitaminosis; amyloidosis; or polyneuropathy of unknown aetiology) were excluded. QST, quantitative sensory testing; CIN, chemotherapy-induced neuropathy.

Table 1
Epidemiologic, clinical and therapeutic data of the study population.

	RestP	MovP	MovP+RestP	Painful CIN	NonP	All
Age (years)	60.0 ± 1.6	57.0 ± 2.4	54.5 ± 1.8	57.4 ± 1.1	55.4 ± 1.1	56.2 ± 0.8
Patients (n)	25 (17.1%)	15 (10.3%)	21 (14.4%)	61 (41.8%)	85 (58.2%)	146 (100%)
Gender	M: 7 (28%) F: 18 (72%)	M: 2 (13%) F: 13 (87%)	M: 3 (14%) F: 18 (86%)	M: 12 (24.5%) F: 49 (75.5%)	M: 34 (40%) F: 51 (60%)	M: 46 (31.5%) F: 100 (68.5%)
Gender ratios (F/M) [a]	2.6/1	6.5/1	6.0/1	4.1/1	1.5/1	2.2/1
Clinical impairment score [b]	7.8 ± 0.5	5.5 ± 0.6*	6.8 ± 0.5	6.93 ± 0.3	6.9 ± 0.3	6.9 ± 0.2
Diagnoses						
Gastrointestinal cancer	13 (52.0%)	3 (20.0%)	7 (33.3%)	23 (37.8%)	43 (50.6%)	66 (45.2%)
Colon cancer	13	3	7	23	38	61
Gastric cancer	0	0	0	0	2	2
Esophageal cancer	0	0	0	0	3	3
Gynaecological cancers	7 (28.0%)	11 (73.3%)	10 (47.6%)	28 (45.9%)	22 (25.9%)	50 (34.2%)
Ovarian cancer	3	4	3	10	10	20
Breast cancer	4	7	6	17	11	28
Uterine cancer	0	0	1	1	1	2
Hematologic cancers	3 (12.0%)	1 (6.7%)	3 (14.3%)	7 (11.5%)	18 (21.2%)	25 (17.1%)
Hodgkin's lymphoma	0	1	0	1	7	8
Non-Hodgkin lymphoma	3	0	2	5	10	15
Leukemia	0	0	1	1	1	2
Cancer of unknown primary (CUP)	2 (8.0%)	0 (0%)	0 (0%)	2 (3.3%)	2 (2.4%)	4 (2.7%)
Lung cancer	0 (0%)	0 (0%)	1 (4.8%)	1 (1.6%)	0 (0%)	1 (0.7%)
Chemotherapy						
Platinum derivatives	19	7	13	39 (63.9%)	56 (65.9%)	95
Oxaliplatin	14	3	7	24	38	62
Carboplatin	5	4	4	13	13	26
Cisplatin	0	0	2	2	5	7
5-fluorouracil and derivatives	15	5	11	31 (50.8%)	45 (52.9%)	76
5-FU	15	5	10	30	41	71
Capecitabine	0	0	1	1	4	5
Taxanes	7	10	8	25 (41.0%)	22 (25.9%)	47
Paclitaxel	7	8	6	21	13	34
Docetaxel	0	2	2	4	9	13
Anthracyclines	4	7	8	19 (31.1%	28 (32.9%)	47
Doxorubicin	1	2	2	5	22	27
Epirubicin	3	5	6	14	6	20
Vinca alkaloids	2	1	3	6 (9.8%)	17 (20.0%)	23
Vincristine	2	1	2	5	17	22
Vinorelbine	0	0	1	1	0	1
Monoclonal antibodies	1	2	3	6 (9.8%)	8 (9.4%)	14
Trastuzumab	0	2	0	2	0	2
Rituximab	0	0	3	3	7	10
Bevacizumab	1	0	0	1	1	2
Others	6	9	11	26 (42.6%)	48 (56.5%)	74
Cyclophosphamide	5	7	8	20	29	49
Etoposide	0	1	2	3	8	11
Bleomycin	0	1	0	1	5	6
Procarbazine	0	0	0	0	5	5
Fludarabine	0	0	1	1	0	1
Bortezomib	1	0	0	1	0	1
Gemcitabine	0	0	0	0	1	1
Interval (end of chemotherapy to 1st study visit) [c]	8.0 ± 1.6 months	4.1 ± 1.2 months	7.0 ± 1.7 months	6.7 ± 0.9 months	4.4 ± 0.6 months	5.4 ± 0.6 months

[a] Within the painful chemotherapy-induced neuropathy (CIN) subgroups, the sex ratio in the RestP subgroup was comparable to the painless (NonP) CIN subgroup (F/M: 2.6/1, ie, 72% females, $\chi^2 = 1.19$, $df = 1$, ns), however, the sex ratio in the MovP and MovP+RestP group was shifted to the female sex (MovP: 6.5:1, ie, 85.7%; $\chi^2 = 3.94$, $df = 1$, $P = 0.08$ (ns); MovP+RestP: 6:1; ie, 87.7%; $\chi^2 = 4.99$, $df = 1$, $p = 0.04$).

[b] Mean clinical impairment score in the 4 CIN subgroups is presented because no change was observed between the initial assessment and the follow-up [$F(1, 142) = 0.17$; $P = 0.68$]; significant subgroup differences were found [$F(3, 142) = 3.057$; $P < 0.05$] with $^*P < 0.05$, indicating significant differences between the RestP and the MovP subgroups.

[c] The latency between the end of the chemotherapy and the enrolment in our study was longer in patients with painful CIN compared to patients with painless CIN (6.7 ± 0.83 vs 4.4 ± 0.71 months, $P < 0.05$).

1) No pain (Non Pain group, NonP)
2) Ongoing pain at rest (eg, pain occurred predominantly while sitting or lying and improved during activity) (Resting Pain group, RestP)
3) Pain exclusively while walking and standing but disappearing at rest (eg, while sitting or lying) (Movement Pain group, MovP)
4) Both types of pain (ie, ongoing pain at rest and movement-associated pain) (MovP+RestP) (Fig. 1).

For stratification, data were independently evaluated by 2 clinicians (C.E., B.B.). Further pain characteristics were assessed using the McGill Pain Questionnaire (see also Section 2.7).

2.3. Clinical assessment

All patients were examined by a neurologist (C.G.). Sensory testing assessed mechanical pain sensation (toothpick), touch (Q-tip), and vibration (64-Hz tuning fork, malleolus medialis); motor

examination assessed weakness and muscle atrophy and deep tendon reflexes.

Sensory and motor findings were given a modified deficit score (modified from [63]) with a total of 10 points. Polyneuropathy was classified as mild (3–5 points), moderate (6–8 points), or severe (9–10 points).

- Triceps surae reflex: normal (0), impaired (1 point/side), and absent (2 points/side) (ie, maximum: 4 points)
- Pallanesthesia or pallhypesthesia were assessed at the lateral malleoli. Normal values (20–40 years: ⩾5/8; 41–60 years: ⩾4.5/8, and 61–80 years: ⩾4/8) were scored 0 points/side. Abnormal values were scored 1 point/side (maximum: 2 points)
- Normal tactile sensation and pain perception (toothpick) were assessed at the foot dorsum and each scored 0 points/side; hypesthesia and hypalgesia were each scored 1 point/side (ie, maximum: 4 points).

Additionally, myofascial trigger points in the tibialis anterior and gastrocnemius muscles [52] were routinely assessed.

2.4. Nerve conduction studies

Motor (peroneal and ulnar) and sensory (sural and ulnar nerve) nerve conduction was assessed on the right side of the body. Reference data were taken from our own laboratory [32]: compound motor action potentials >4 mV (peroneal and ulnar nerve), sensory nerve action potentials >4 μV (sural nerve) or >10 μV (ulnar nerve), nerve conduction velocities >40 m/s (lower extremity) and >45 m/s (upper extremity). Skin temperature was kept >32°C. Data are presented in Supplementary Table 1.

2.5. Quantitative sensory testing

Quantitative sensory testing (QST) was performed on the right foot dorsum. In the first session, the test area was marked and photo-documented to identify the site during follow-up.

Skin and muscle sensitivity was tested using the standardized test battery for QST [25,49]. QST assessed the function of small and large afferent fibres. The standardized assessment contained 13 different thermal and mechanical tests. In brief, the following parameters were tested: thermal detection thresholds for the perception of cold (CDT: cold detection threshold) and warmth (WDT); paradoxical heat sensations during the procedure of alternating warm and cold stimuli (thermal sensory limen); thermal pain thresholds for cold (CPT: cold pain threshold) and hot stimuli (HPT); mechanical detection thresholds for touch (MDT) and vibration (VDT); mechanical pain sensitivity including thresholds for pinprick (MPT: mechanical pain threshold) and blunt pressure (PPT: pressure pain threshold); a stimulus–response function for pinprick sensitivity (MPS: mechanical pain sensitivity); and dynamic mechanical allodynia (DMA) as well as pain summation to repetitive pinprick stimuli (wind-up ratio). For all parameters, negative (loss of function) as well as positive (gain of function) phenomena were assessed.

2.6. Classification of polyneuropathy

We differentiated between large-, small-, and mixed-fibre neuropathy. Pathologic nerve conduction, impaired tactile or vibration detection thresholds (MDT, VDT) in QST were considered indicative of large-fibre neuropathy, while impaired cold and warm detection (CDT, WDT) or increased mechanical pain thresholds (pressure pain [PPT]) and pinprick pain [MPT]) indicated small-fibre involvement. Involvement of both fibre classes indicated mixed-fibre neuropathy [6,44].

2.7. Pain drawings, pain questionnaire, and psychometric assessment

2.7.1. Pain drawings

Patients with pain filled in a standardized pain drawing. Individual pain drawings were scanned and superimposed using Photoshop CS (version 8.01, Adobe Systems Inc, San Jose, CA, USA). All pain localizations indicated by the patients were taken into consideration.

2.7.2. Pain and psychometric assessment

Pain was quantified using the McGill Pain Questionnaire (MPQ, German version) [53]. All patients were asked to fill in the Hospital Anxiety and Depression Scale (HADS; German version) [31]. The HADS cutoff criteria were defined at ⩾8 (possible cases) and ⩾11 (probable cases).

2.8. Re-evaluation of patients (follow-up)

At the follow-up session after 17 days, all patients (n = 146) were assessed again using QST, HADS, MPQ, and pain drawings. Selective neurography of the sural nerve was performed, where it had not been obtained at the initial assessment, in order to minimize false-negative results. Between the 2 assessments, patients underwent a standardized rehabilitation programme comprising:

- Physical therapy (twice weekly, 6 × 30 minutes), including training of proprioception and balance
- Occupational therapy (twice weekly, total: 6 × 60 minutes)
- Alternating baths of the upper and lower extremity (twice weekly, total: 6 × 15 minutes)

We did not expect major changes in clinical and electrophysiological parameters (stability assessment), but hypothesized that patients might show changes in pain and anxiety or depression.

2.9. Data evaluation and statistics

2.9.1. QST-data

QST values (exceptions: vibration, cold, and heat pain threshold) were log-transformed in order to achieve normal distribution [49]. Multisite gender, age, and site-adjusted reference values are available from our national pain network [42]. Patients' data were then transformed into a standard normal distribution (*z*-transformation) for each parameter using the following formula:

$$z - \text{value} = \frac{(\text{single value}_{\text{test area}} - \text{mean}_{\text{reference}})}{\text{standard deviation}_{\text{reference}}}$$

Z values >0 indicate an increased sensitivity compared to controls, whereas *z* scores <0 indicate decreased sensitivity.

2.9.2. Statistics

2.9.2.1. Influence of chemotherapy regimen on clinical and neurophysiological parameters. Patients were treated with different chemotherapeutic regimens (Table 2). To evaluate the neurotoxic effects of the regimens, 5 groups were formed (Supplementary Table 2).

A Kruskal-Wallis test was calculated, including the between-subject factor "chemotherapy regimen" to investigate the effects of chemotherapy regimen on somatosensory parameters (QST, nerve conduction studies [NCS]) and on anxiety/depression (HADS). To avoid missing data, pain descriptors were not included, as they were not assessed in painless CIN.

Table 2
Incidence of polyneuropathy according to nerve conduction studies (ulnar, peroneal and sural nerve).

			Frequency of polyneuropathy			Classification of polyneuropathy by involved fibre class			
		n	Nerve conduction studies	QST	Combination	Large	Mixed	Small	Nonclassified[a]
Study population		146	81.5% (119/146) Sensory neuropathy: 48% Sensorimotor neuropathy: 33.5%	78.8% (115/146)	97.3% (142/146)	61.0% (89/146)	34.9% (51/146)	1.4% (2/146)	2.7% (4/146)
Painless CIN		85	84.5% (72/85)	81.2% (69/85)	98.8% (84/85)	65.9% (56/85)	32.9% (28/85)	0% (0/85)	1.2% (1/85)
Painful CIN	Total	61	77.0% (47/61)	75.4% (46/61)	95.1% (58/61)	54.1% (33/61)	37.7% (23/61)	3.3% (2/61)	4.9% (3/61)
	RestP	25	88.0% (22/25)	88.0% (22/25)	100% (25/25)	48% (12/25)	48% (12/25)	4% (1/25)	0% (0/25)
	MovP	15	80.0% (12/15)	53.3% (8/15)	80.0% (12/15)	53.3% (8/15)	26.7% (4/15)	0% (0/15)	20.0% (3/15)
	MovP+RestP	21	62.0% (13/21)	76.2% (16/21)	100% (21/21)	61.9% (13/21)	33.3% (7/21)	4.8% (1/21)	0% (0/21)

QST, quantitative sensory testing; CIN, chemotherapy-induced neuropathy, NCS, nerve conduction studies.
The absolute number is given in brackets. According to NCS and QST, polyneuropathy was classified as large (Aβ-), small (C-, Aδ-) and mixed-fibre neuropathy.
[a] Clinical signs of polyneuropathy but nonpathologic NCS and QST.

2.9.2.2. Analysis of somatosensory parameters (QST) and questionnaires. QST parameters were grouped according to their physiological function:

1) Thermal detection (CDT, WDT).
2) Mechanical detection (MDT, VDT).
3) Thermal hyperalgesia (CPT, HPT).
4) Mechanical hyperalgesia (MPT, PPT).

Analyses of variance, including the within-subject factor "test/retest" (follow-up) and between-subject factors "pain/no pain" were applied to investigate global effects of pain and differences between pain subgroups (NonP, RestP, MovP, and MovP+RestP). Fisher's least-square difference was used for post hoc and simple effect analyses. Comparisons of QST parameters to *z*-normalized reference data were performed employing Simple Interactive Statistical Analysis [42].

Chi-squared test was applied to assess gender differences in painless and painful CIN (including painful subgroups) and the incidence of anxiety and depression (HADS above cutoff).

All data are given as mean ± SEM. *P*-values < 0.05 were regarded as significant. Statistical analyses were performed using Statistica 7.1 (StatSoft, Tulsa, OK, USA).

2.9.3. Discriminant analysis

Stepwise discriminant analyses (minimize Wilks' lambda) were performed to identify predictive discriminators between 1) painful vs painless CIN and 2) patients with ongoing pain (RestP) and patients with a movement-associated pain or pain component (MovP, MovP+RestP). Classification was achieved by calculating Fisher's canonical linear discriminant function.

3. Results

3.1. Confirmation of CIN

The mean clinical impairment score in the study population (n = 146) was 6.9 ± 0.2, suggesting moderate neuropathy. Neuropathy was confirmed by NCS in 81.5% (119 of 146) and by QST in 79% of patients (115 of 146), resulting in 97% of patients (142 of 146) by the combination of both. In 4 patients, both methods failed to confirm neuropathy despite the bilateral absence of the triceps surae reflex.

According to NCS and QST (Table 2), affection of large (Aβ) fibres was most frequent (61.0%, 89/146 patients), followed by mixed-fibre polyneuropathy (34.9%, 51/146). Isolated small- (C-, Aδ-) fibre neuropathy was rare (1.4%, 2/146).

3.2. Influence of chemotherapy regimen on CIN

Applying Kruskal-Wallis analyses, significant differences among the 5 chemotherapy groups were found for large-fibre function parameters: sensory ulnar ($df = 4$; $F = 4.29$; $P < 0.01$), suralis nerve action potential ($df = 4$; $F = 10.64$; $P < 0.001$), and VDT ($df = 4$; $F = 6.38$; $P < 0.001$). The strongest large-fibre impairment was consistently found for platinum-based regimens. There was no effect on the remaining parameters.

Furthermore, the chemotherapy regimen had no significant effect on whether a patient developed painful or painless CIN ($\chi^2 = 7.1$, $P = 0.68$).

3.3. Pain in CIN

Epidemiologic and therapeutic data are presented in Table 2. Eighty-five patients (58%) had painless polyneuropathy and 61 patients (42%) reported chemotherapy-associated pain; 69% of the total study population were women (sex ratio 2.2/1). In painful CIN, this number increased to approximately 80% (sex ratio: 4.1/1, $\chi^2 = 6.80$, $df = 1$, $P < 0.01$).

3.3.1. Painless versus painful CIN

Clinical impairment scores did not differ between painless and painful CIN [$F(1, 144) = 0.015$; n.s.]. Furthermore, the frequency of pathologic NCS and QST was similar in painless and painful CIN (Table 2).

Somatosensory QST profiles also showed no differences between painful and painless CIN (Fig. 1A). They were characterized by impairment of small- (CDT, WDT) and large-fibre function (MDT, VDT, all $P < 0.01$ compared to normal values) combined with hyperalgesia for heat (HPT, $P < 0.01$) and blunt pressure (PPT, $P < 0.05$), indicating nociceptive sensitization. Pin-prick hyperalgesia (MPT, MPS), as a sign of central sensitisation, was not found in either group. Moreover, there was no clinically relevant DMA in the painful CIN group (Fig. 2A).

3.3.1.1. Anxiety and depression (HADS questionnaire). A higher percentage of patients with painful CIN was above the HADS cutoff score ($\geqslant 8$) for anxiety and depression, as compared to painless CIN. In the follow-up, anxiety and depression decreased significantly (Table 3).

3.3.2. Patient stratification and subgroup analyses

Among the patients with painful CIN, 25 (41%) patients were classified as RestP, 15 (25%) as MovP, and 21 (34%) as MovP+RestP (Table 1). According to a proposed grading scheme for neuropathic pain [21,56], all patients with painful CIN fulfilled the criteria of

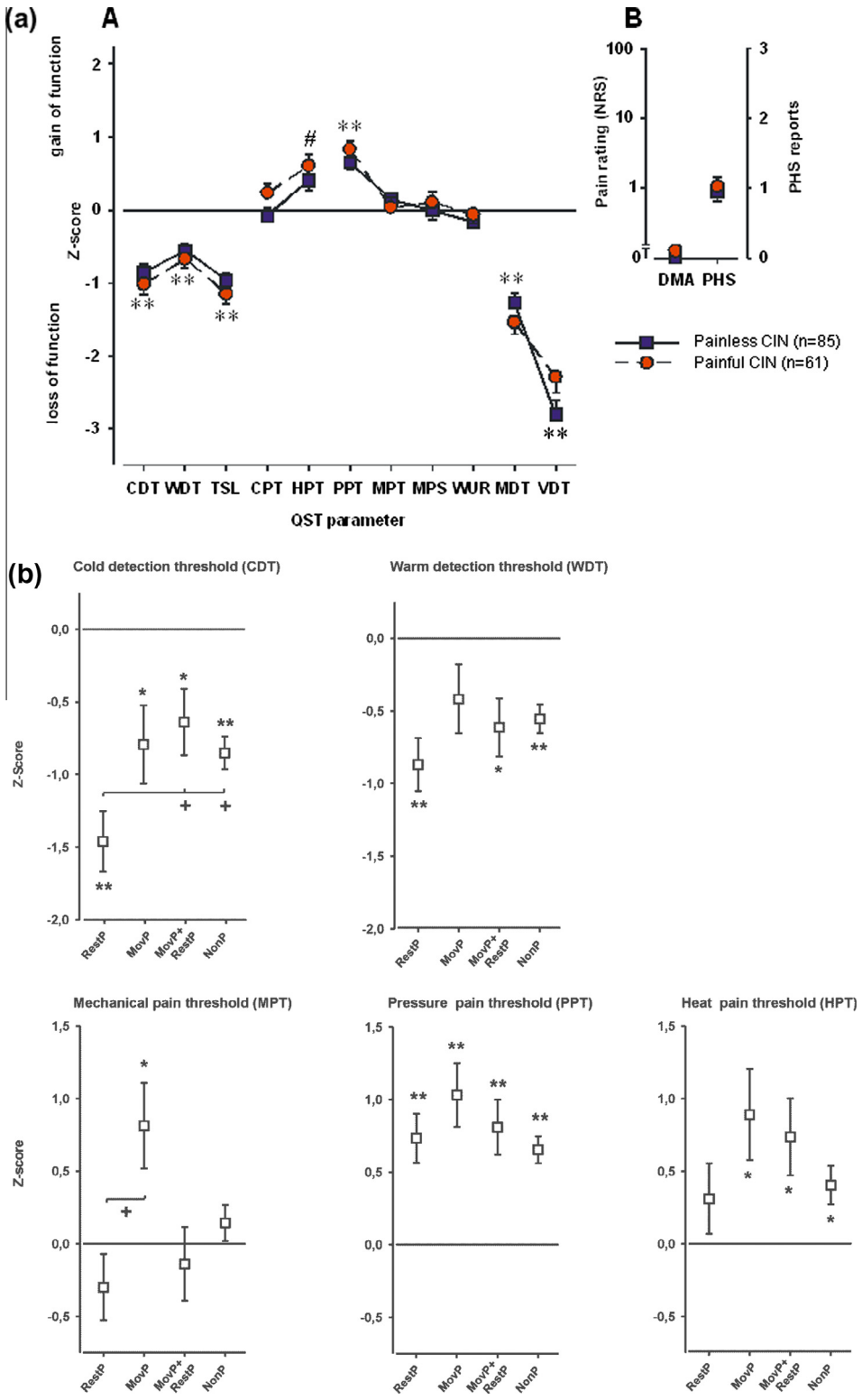

Fig. 2. Somatosensory profiles in painless and painful chemotherapy-induced neuropathy (CIN) (quantitative sensory testing [QST]) (A) and somatosensory characteristics in the CIN subgroups (B) are presented. (A) Somatosensory profiles of the painless and painful CIN group are presented. In the follow-up, warm detection threshold (WDT) [$F(1, 144) = 8.17$; $P < 0.01$], cold pain threshold (CPT) [$F(1, 144) = 8.80$; $P < 0.01$], and vibration detection threshold (VDT) [$F(1, 144) = 4.55$; $P < 0.05$] marginally improved due to congruent changes in the painful and painless CIN group (interaction "group∗retest": WDT: [$F(1, 144) = 0.67$]; CPT: [$F(1, 144) = 0.074$]; VDT: [$F(1, 144) = 1.04$]; all ns). Data of both assessments are therefore combined. About 20% (n = 12/61) of patients with painful CIN reported dynamic mechanical allodynia (DMA). The pain intensity (numerical rating scale) of this touch-provoked pain was marginal and not clinically relevant in these patients. Wind-up ratio (WUR) could not be assessed in all patients (see [23]) and was therefore not included in the statistical analysis. Thermal sensory limen (TSL) as a compound parameter (cold detection threshold [CDT] and WDT) is included in the QST protocol to evoke paradoxical heat sensations (PHS). *Z*-scores are presented but are excluded from statistical analysis to avoid redundant information. Significant group differences compared to reference data are indicated: $^{**}P < 0.01$: painful and painless CIN; $^{\#}P < 0.01$ in painful and $P < 0.05$ in painless CIN. (B) Somatosensory parameters in subgroups of CIN. $^{*}P < 0.5$, $^{**}P < 0.01$: significant differences compared to normative data (*z*-value = 0); $^{+}P < 0.05$: significant differences between subgroups. NRS, numerical rating scale; MPS, mechanical pain sensitivity; MDT, mechanical detection threshold; VDT, vibration detection threshold.

Table 3
Data of the McGill Pain Questionnaire (MPQ) in the subgroups of patients with painful CIN (RestP, MovP, MovP+RestP).

	Anxiety				Depression		
Score (0–21)	Painless (n = 65)	5.86 ± 0.48		F(1, 119) = 9.46; $P < 0.01$	4.28 ± 0.41		F(1, 119) = 5.83; $P < 0.05$
	Painful (n = 56)	8.03 ± 0.52			5.72 ± 0.44		
	Test (n = 121)	7.30 ± 0.38		F(1, 119) = 12.02; $P < 0.001$	5.26 ± 0.31		F(1, 119) = 9.55; $P < 0.01$
	Retest (n = 121)	6.43 ± 0.39			4.64 ± 0.33		
Cutoff score ($\geqslant$ 8)	Anxiety				Depression		
		Painless (n = 65)	Painful (n = 56)		Painless (n = 65)	Painful (n = 56)	
	Test (n = 121)	36.9% (24/65)	55.4% (31/56)	$\chi^2 = 4.12$, $df = 1$, $P < 0.05$	13.8% (9/65)	30.4% (17/56)	$\chi^2 = 4.86$, $df = 1$, $P < 0.05$
	Retest (n = 121)	29.2% (19/65)	53.6% (30/56)	$\chi^2 = 7.40$, $df = 1$, $P < 0.01$	12.3% (8/65)	32.1% (18/56)	$\chi^2 = 7.02$, $df = 1$, $P < 0.05$

CIN, chemotherapy-induced neuropathy.

"probable" or "definite" neuropathic pain (NeuP); all patients in the RestP group (n = 25) and most patients in the MovP (13/15, 87%) or MovP+RestP group (20/21, 95%) fulfilled the criterion "definite NeuP." Three patients (MovP, n = 2, MovP+RestP, n = 1) fulfilled the criterion "probable NeuP," which is characterized by clinical signs suggestive of neuropathy without confirmation of neuropathy in apparative tests such as nerve conduction studies or QST.

Pain patterns remained stable in the follow-up: all patients with painless CIN remained pain free, and 59 of the 61 pain patients (97%) still reported pain. Three patients in the MovP+RestP subgroup reported movement-associated pain only and 2 presented with pain at rest only. One patient from the RestP subgroup developed additional movement-associated pain and one patient in the MovP subgroup developed pain at rest. In total, only 9 of 146 patients (6%) changed their pain characteristics.

3.3.2.1. Pain drawings. The pain drawings of patients in the 3 pain subgroups (RestP, MovP, MovP+RestP) were superimposed on each other (Fig. 3). The colour intensity reflects the number of patients that experienced pain in this area. In the RestP subgroup, the distribution of pain in the extremities corresponded best to the distal-symmetric pattern of sensory loss. This pattern was less prominent in the MovP and MovP+RestP subgroups. Pain that was indicated over muscles corresponded either to diffuse muscle pain or to myofascial trigger points, with additional referred pain in the manual examination (Fig. 1). In particular, active trigger

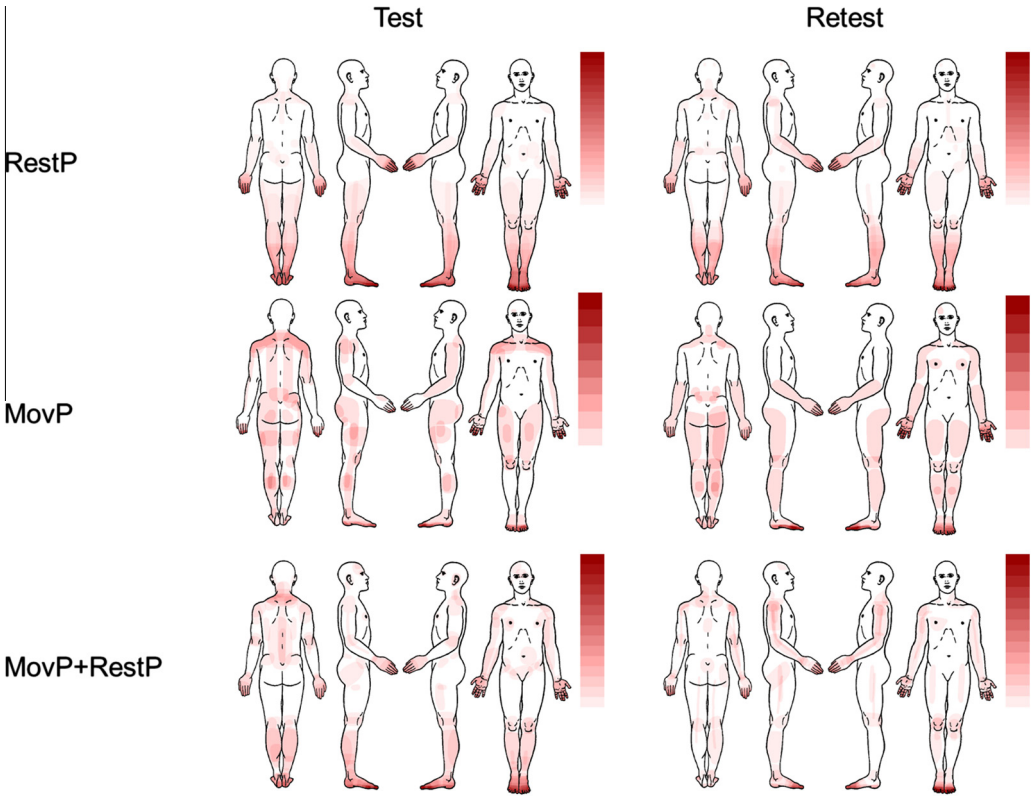

Fig. 3. Superimposed pain drawings of the patients with painful chemotherapy-induced neuropathy (CIN) (RestP, MovP, MovP+RestP) at both assessment times. The colour intensity reflects the number of patients with pain in the respective area (all pain localisations indicated by the patients were considered). In the RestP subgroup, the distribution of pain corresponded best to the distal-symmetric distribution of their sensory loss. This pattern was less prominent in patients in the MovP and MovP+RestP subgroup. In the MovP subgroup, some patients indicated circumscriptive areas of pain over muscles corresponding to myofascial trigger points. Pain localized in the more proximal body parts or the trunk was more frequent in the MovP and MovP+RestP subgroup but was not regarded a consequence of chemotherapy.

points were found in 3 patients in the MovP and 6 patients in the MovP+RestP subgroup.

3.3.2.2. Clinical impairment scores. Clinical impairment scores differed among the 4 CIN subgroups [$F(3, 142) = 3.05$; $P < 0.05$]: patients in the RestP subgroup were most impaired (Table 1).

3.3.2.3. QST sensory patterns in subgroups of CIN. Differences [$F(3, 142) = 2.93$; $P < 0.05$] among the 4 CIN subgroups were found: CDT was more impaired in the RestP ($z = -1.46 \pm 0.21$) compared to the MovP+RestP ($z = -0.64 \pm 0.23$; $P < 0.01$) and the NonP group ($z = -0.85 \pm 0.11$; $P = 0.01$), and marginally impaired compared to the MovP group ($z = -0.79 \pm 0.27$; $P = 0.05$; see Fig. 2B). Additionally, mechanical pinprick hyperalgesia varied among the subgroups [MPT; $F(3, 142) = 3.30$; $P < 0.05$]. The MovP group was more sensitive compared to the RestP ($z = -0.30 \pm 0.23$, $P < 0.01$) and the MovP+RestP group ($z = -0.14 \pm 0.26$; $P < 0.05$). Exclusion of patients under pain medication (n = 6) did not influence this result [MPT; $F(3, 136) = 3.42$; $P < 0.05$].

All other thermal and mechanical detection [WDT: $F(3, 142) = 0.99$; MDT: $F(3, 142) = 2.18$; and VDT: $F(3, 142) = 1.19$] and pain thresholds [CPT: $F(3, 142) = 0.78$; HPT: $F(3, 142) = 1.15$, PPT: $F(3, 142) = 0.91$] did not differ among the subgroups.

3.3.2.4. Anxiety and depression in subgroups of painful CIN. HADS anxiety scores differed among the 4 CIN subgroups [$F(3, 117) = 4.15$; $P < 0.01$], with the highest ratings in the MovP+RestP group (Supplementary Fig. 1). The reduction of anxiety [$F(3, 117) = 10.4$; $P < 0.01$] in the follow-up was mainly driven by reduction in the MovP (−16.2%, $P = 0.05$), MovP+RestP (−12.9%, $P < 0.05$), and NonP groups (−13.2%, $P < 0.05$), but not in the RestP group (−3.5%, ns).

Depression scores did not differ among the CIN groups and decreased in the follow-up [$F(1, 117) = 7.2$; $P < 0.01$] without subgroup differences [$F(3, 117) = 2.3$; $P = 0.08$].

3.3.2.5. Pain questionnaire (McGill). The McGill Pain Rating Index was similar in the 3 pain subgroups [$F(1, 52) = 0.43$; n.s.] and decreased in the follow-up [$F(1, 52) = 4.16$; $P < 0.05$] without subgroup differences (Table 4). The McGill Present Pain Intensity score also decreased in the follow-up [$F(1, 44) = 6.52$; $P < 0.05$], mainly due to subgroup-specific changes [interaction "pain-subgroup∗follow-up" $F(2, 44) = 3.29$; $P < 0.05$] in the MovP (−19.5%, $P = 0.07$) and MovP+RestP (−24.1%, $P < 0.01$), but not in the RestP subgroup (+2.4%, n.s.).

3.3.2.6. The multivariate approach – discriminant analysis. Stepwise discriminant analysis revealed that only the HADS-A score contributed to discrimination between patients with painful and painless CIN. The discriminant function was −1.750 + 0.245∗HADS-A. Values < 0 predict painless and >0 painful CIN. Fishers' classification revealed correct grouping in 66% by HADS-A alone.

To analyse the pain subgroups, patients were regrouped for statistical reasons due to their limited number (n = 61): RestP vs. "movement-associated pain component" (ie, "MovP" and "MovP+RestP"). The HADS-A and deafferentation for Aδ fibres (CDT) contributed to the discrimination between the 2 groups. Correct classification was possible in 69% by the discriminant function −0.556 + 0.935 CDT z score +0.177 HADS-A. Values <0 indicated RestP and values >0 "movement-associated pain component."

4. Discussion

The main findings of this study are that:

1) Chemotherapy affects all classes of nerve fibres. Compared to large- (61%) and mixed-fibre polyneuropathy (35%), isolated small-fibre neuropathy is very rare (1.4%).
2) QST and NCS do not differentiate between painful and painless CIN. However, "anxiety" does.
3) Although CIN-associated pain is usually regarded as neuropathic [19], our study demonstrates some heterogeneity: movement-associated pain in approximately 60% of patients points to a musculoskeletal pain component. This subgroup presented with different clinical, somatosensory, and psychological parameters.

4.1. Characterisation of neuropathy

According to previous studies [62], CIN was predominantly sensory and of moderate severity. Nerve conduction verified large-fibre polyneuropathy [18] and QST small-fibre loss or sensitization [48]. Combining both methods, polyneuropathy was confirmed in

Table 4
Data of the McGill Pain Questionnaire (MPQ) and its subscales (PRI, NWC and PPI) are presented in the subgroups of patients with painful CIN (RestP, MovP, MovP+RestP).

MPQ		RestP	MovP	MovP+RestP	Painful CIN	Test-retest	Group effect
Patients (NWC, PRI)		n = 23	n = 13	n = 19	n = 55		
Number of words chosen (NWC)	Test	9.6 ± 1.1	9.2 ± 1.7	10.4 ± 1.2	9.8 ± 0.7		n.s.
	Retest	9.1 ± 1.2 (−4.9%)	7.5 ± 1.6 (−18.3%)	9.8 ± 1.5 (−5.0%)	9.0 ± 0.8 (−8.2%)	n.s.	
Pain rating index (PRI)	Test	23.0 ± 2.9	20.8 ± 4.0	23.9 ± 3.2	22.8 ± 1.9		n.s.
	Retest	22.2 ± 3.2 (−3.4%)	16.1 ± 3.6 (−22.6%)	19.9 ± 3.5 (−16.7%)	20.0 ± 2.0 (−12.3%)	$P < 0.05$	
Sensory	Test	14.1 ± 1.7	13.4 ± 2.6	15.5 ± 1.7	14.4 ± 1.1		n.s.
	Retest	14.5 ± 1.9 (+2.8%)	10.0 ± 2.2 (−25.4%)	12.3 ± 2.0 (−20.7%)	12.7 ± 1.2 (−11.8%)	n.s.	
Affective	Test	1.9 ± 0.5	2.3 ± 0.7	2.5 ± 0.7	2.2 ± 0.3		n.s.
	Retest	1.7 ± 0.5 (−6.9%)	1.6 ± 0.7 (−29.9%)	3.5 ± 0.8 (+37.2%)	2.3 ± 0.4 (+5.0)	n.s.	
Emotional	Test	1.9 ± 0.4	1.2 ± 0.4	1.7 ± 0.4	1.7 ± 0.2		n.s.
	Retest	1.5 ± 0.3 (−23%)	0.6 ± 0.3 (−50%)	1.4 ± 0.4 (−18.4%)	1.3 ± 0.2 (−23.5%)	$P < 0.05$	
Miscellaneous	Test	5.1 ± 0.7	4.1 ± 1.0	4.2 ± 0.8	4.5 ± 0.5		n.s.
	Retest	4.5 ± 0.9 (−11.8%)	3.8 ± 0.9 (−5.6%)	3.5 ± 0.8 (−16.6%)	4.0 ± 0.5 (−11.1%)	n.s.	
Patients (PPI)		n = 18	n = 11	n = 18	n = 47		
Present pain intensity (PPI)	Test	2.5 ± 0.2	2.8 ± 0.3	2.8 ± 0.2	2.7 ± 0.1		n.s.
	Retest	2.6 ± 0.2 (+2.4%)	2.3 ± 0.3 (−19.5%)	2.1 ± 0.3 (−24.1%)	2.3 ± 0.2 (−12.7%)	$P < 0.05$	

PRI, Pain Rating Index; NWC, Number of words chosen; PPI, present pain intensity; CIN, chemotherapy-induced neuropathy; n.s., not significant.

about 97% of patients, mainly by additional detection of small-fibre impairment.

4.2. Effect of chemotherapy regimen on CIN

Different chemotherapeutic regimens might induce different symptoms; for example, acute hyperexcitability and cold hyperalgesia have been described following oxaliplatin therapy [10,37]. Our patients were examined several months (mean >6 months) after chemotherapy. Consistent with previous data [3], we found sensory loss across all fibre types (NCS, QST); that is, acute nerve fibre hyperexcitability shortly after treatment may turn into nerve fibre degeneration in chronic CIN. Chemotherapeutic protocols regularly comprised a combination of chemotherapeutics. Therefore, specific symptoms and signs could not be attributed to an individual substance. The 5 major chemotherapy groups impacted differently on large- but not on small-fibre function or pain.

Somatosensory profiles (QST) in painful and painless CIN were identical. A large overlap of somatosensory changes has been described, for example, in painful and painless postherniotomy neuropathy [1,27]. Even on a structural and molecular level, a "biomarker" for pain has not yet been identified [50].This might be due to the heterogeneity of pain mechanisms [22,47]. However, consistent with previous studies [57], the anxiety and depression scores were higher in patients with painful CIN, and anxiety was the only significant discriminator in our multivariate approach. This underscores the importance of the affective state for chronic pain. It is still unclear, however, whether the mood disturbances cause pain, or vice versa [7].

4.3. Identification of pain subgroups in CIN

Neuropathic pain is a direct consequence of a lesion or disease of the somatosensory system. As provided by a grading scheme, diagnostic safety can be achieved by unequivocal history, anatomically plausible pain distribution, and clinical and apparative findings [21,56]. Applying this scheme, all patients in the study reached the levels of "definite" (95%) or "probable" (5%) neuropathic pain [56]: patients with painful CIN have 1) a conclusive history of a peripheral nerve lesion and a distal pain distribution fitting with polyneuropathy, and 2) clinically and/or electrophysiologically verified nerve lesions.

Symptoms of neuropathic pain are variable, suggesting that there can even be different neuropathic pain mechanisms in one disease [44]. In individual patients it might even be difficult to differentiate whether pain is primary (neuropathic) or secondary (ie, triggered by neuropathy) to the nerve lesion. This particularly applies for radiating pain, which could be either a pain projection into the innervation territories of damaged nerves or referred pain from deep somatic structures such as muscles [24,40,43,60], for example, pain associated with spasticity, flaccid pareses, or rigor (eg, in Parkinson disease) [29,59]. Impaired motor function leads to altered movement patterns and subsequent musculoskeletal pain that is typically aggravated by walking and reduces or disappears at rest (eg, arthrosis of ankles and toes or myofascial pain). Sensory neuropathy can also lead to unphysiological movement patterns by impairment of proprioception. An unsteady gait, for example, will lead to repetitive strains of muscles, bones, and joints [24]. Subsequently, patients develop an increased risk of falls, which may result in a fearful gait characterized by increased muscle tension and overload [45,55].

4.4. Characteristics of neuropathic and musculoskeletal pain

In agreement with recent data [34], the prevalence of pain in our study was more than 40%. Patients reported "ongoing pain at rest," movement-associated pain, or both. Pain descriptors (MPQ) did not allow for a differentiation. As indicated above, one characteristic of musculoskeletal pain is its association with weight bearing or physical exercise [45,54]. In contrast, persisting pain at rest or at night that alleviates while walking is a characteristic of neuropathic pain [9]. We employed this straightforward differentiation to subgroup our patients, being aware of its imprecision. Nevertheless, this differentiation will increase the likelihood of a predominant pain component. Our results support this view as follows:

1) These 2 types of pain were reflected by differences in the pain drawings: in the RestP subgroup, the distribution of pain resembles the stocking-like distal-symmetric pattern of sensory impairment [56]. In the MovP and MovP+RestP groups, pain distribution was not accompanied by a graded increase of pain. Localized areas of pain over musculature corresponding to myofascial trigger points [52] were depicted only by patients in the MovP and MovP+RestP subgroups (9/36 patients).
2) In the RestP subgroup, the somatosensory profile (QST) indicates small-fibre deafferentation and only marginal hyperalgesia, most likely because the nerve fibre loss prevents stimulus-related hyperalgesia [44]. On the contrary, the MovP group was characterized by the opposite: mechanical hyperalgesia (MPT) and less small-fibre loss. The somatosensory profile of the MovP+RestP subgroup featured characteristics of both.
3) Anxiety was higher in the patients with musculoskeletal pain components (MovP, MovP+RestP). Anxiety is a known risk factor for musculoskeletal pain [45]. It activates the sympathetic nervous system and the release of stress hormones [36]. This, in turn, could lead to an impairment of muscle spindle functioning [30] that is essential for the control of movements and posture [11].
4) The unbiased multivariate analyses supported the impairment of cold detection threshold – a marker of small-fibre (Aδ) function with pathophysiological implications in neuropathic pain [38,44] – and anxiety as being relevant for differentiation between patients with neuropathic (RestP) and musculoskeletal pain components (MovP, MovP+RestP).

4.5. Limitations

We are aware that our study has some limitations:

1) Preexisting pain medication was not withdrawn. Antineuropathic medication such as calcium channel modulators may suppress mechanical hyperalgesia (indicated by MPT). However, the exclusion of patients under regular pain medication (n = 6) did not influence the significant difference in mechanical hyperalgesia between painful CIN subgroups.
2) We cannot differentiate whether the overrepresentation of women (F/M: >6/1) in the subgroups with musculoskeletal pain is explained by female proneness to musculoskeletal pain (such as, eg, in fibromyalgia or temporomandibular disorders [12,61]) or by the chemotherapeutics (predominantly taxanes) used to treat gynaecological tumours.
3) Musculoskeletal pain is an umbrella term that includes myofascial pain, arthrosis, fasciitis, or muscle cramps alone or, in our patients, in combination with suggested musculoskeletal pain components (MovP, MovP+RestP). Alternatively, muscle pain could be a direct consequence of neuropathy-related motor nerve hyperexcitability or sensitization of afferent muscle or bone fibres (deep somatic hyperalgesia) [15,58], as suggested by the presence of skin mechanical

hyperalgesia in the patient groups with movement-associated pain. Therefore, further studies with rigorously defined patient groups and predefined end points should be performed.

4) We are aware that our patient stratification is not absolute and our study is preliminary, however, it might be stimulating for a more comprehensive view on pain in neuropathy. Highlighting the potential relevance of our clinical classification, only a few patients changed their pain characteristics. Since pharmacotherapy was not altered, physiotherapy (applied to all patients) most likely accounts for this variation. Physiotherapy reduced anxiety and pain mainly in these subgroups with suspected musculoskeletal pain components (MovP, MovP+RestP).

4.6. Conclusion

The results of this study might be stimulating in addressing a long-neglected problem: the possibility of nonneuropathic pain in neuropathy. Treatment of nonneuropathic and neuropathic pain differs substantially: while treatment of neuropathic pain is a domain of pharmacotherapy [4], nonneuropathic pain can be treated by physiotherapy or behavioural training [26,39]. Theoretically, a negative outcome of clinical trials in CIN of otherwise efficacious antineuropathic drugs could be due to nonneuropathic pain components [4,13,28]. Conversely, the initial efficacy of nonsteroidal antiinflammatory drugs in some neuropathies [16,33] might be due to nonneuropathic (eg, musculoskeletal) pain components. It could be suggested that our findings in CIN could be extended to other polyneuropathies as well (eg, diabetic neuropathy). Therefore, our data encourage a careful neurological, psychological, and also manual-therapeutic examination of patients with peripheral neuropathy and pain in order to facilitate successful pain treatment.

Conflict of interest

The authors report no conflict of interest.

Acknowledgements

This paper contains parts of the doctoral theses of B.B. and C.E. Thanks to Martin Dettling for expert technical assistance. This study was supported by the "Arbeitsgemeinschaft für Krebsbekämpfung der Träger der gesetzlichen Kranken- und Rentenversicherung NRW" to T.V., the "Foundation Rhineland – Palatinate, project 936," the NHMRC Australia, the Murdoch University, Perth, Australia, and the German Research Foundation (Bi579/8-1) to F.B. and the "Kalkhof-Rose-Stiftung" to C.G. We would like to thank C. Dietz for reading the manuscript as a native speaker.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2013.08.028.

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