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RESEARCH REPORT

Somatosensory profiling of patients undergoing alcohol withdrawal: Do neuropathic pain and sensory loss represent a problem?

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Abstract

Introduction: Chronic heavy alcohol use is known to cause neurological complications such as peripheral neuropathy. Concerning the pathophysiology, few sural nerve and skin biopsy studies showed that small fibers might be selectively vulnerable to degeneration in alcohol-related peripheral neuropathy. Pain has rarely been properly evaluated in this pathology. The present study aims at assessing pain intensity, potential neuropathic characteristics as well as the functionality of both small and large nerve sensitive fibers.

Methods: In this observational study, 27 consecutive adult patients, hospitalized for alcohol withdrawal and 13 healthy controls were recruited. All the participants underwent a quantitative sensory testing (QST) according to the standardized protocol of the German Research Network Neuropathic Pain, a neurological examination and filled standardized questionnaires assessing alcohol consumption and dependence as well as pain characteristics and psychological comorbidities.

Results: Nearly half of the patients (13/27) reported pain. Yet, pain intensity was weak, leading to a low interference with daily life, and its characteristics did not support a neuropathic component. A functional impairment of small nerve fibers was frequently described, with thermal hypoesthesia observed in 52% of patients. Patients with a higher alcohol consumption over the last 2 years showed a greater impairment of small fiber function.

Discussion: Patients report pain but it is however unlikely to be caused by peripheral neuropathy given the non-length-dependent distribution and the absence of neuropathic pain features. Chronic pain in AUD deserves to be better evaluated and managed as it represents an opportunity to improve long-term clinical outcomes, potentially participating to relapse prevention.

KEYWORDS
alcohol-related peripheral neuropathy, chronic pain, quantitative sensory testing QST

1 | INTRODUCTION

Chronic heavy alcohol use is known to cause neurological complications such as central nervous system degeneration and peripheral neuropathy.[1] Lettsom first described hypoesthesia and paralysis associated with alcohol intake mostly in the lower limbs in 1787.[2] The pathogenesis of alcohol-related peripheral neuropathy is debated and is likely to be multifactorial, including a direct toxicity of alcohol or impurities in alcoholic beverages, nutritional and vitamin deficiency (especially thiamine and B12), hepatic cirrhosis, and altered glucose metabolism.[3–6] A systematic review estimated a pooled prevalence of peripheral neuropathy of 44.2% (CI 35.9%–53%) in patients suffering from alcohol use disorder (AUD) based on history and examination and of 46.3% (CI 35.7%–57.3%) based on nerve conduction studies.[7]

Pain has rarely been evaluated in alcohol-related peripheral (either small or large fiber) neuropathy. In fact, a large systematic review and meta-analysis underlined that only 5/87 studies on alcohol-related peripheral neuropathy reported on pain outcomes.[7] The five studies reporting on pain allow to calculate a pooled estimated prevalence of pain in alcohol-related peripheral neuropathy of 42% (CI 29%–56%, $n = 325$). Of note that these studies considered pain as a dichotomous factor (present or absent), hence failing to report further details on pain intensity, characteristics, functional impact and associated behavior. A neuropathic origin of pain is therefore not established in alcohol-related peripheral neuropathy.

Alcohol-related peripheral neuropathy involves large and small nerve fibers but relative damage of large vs small fibers varies between studies.[4,8] Sural nerve biopsies showed that small fibers might be selectively vulnerable to degeneration in alcohol-related peripheral neuropathy.[4,5,8] Furthermore, skin biopsy analyses revealed a reduced epidermal nerve fiber density in heavy alcohol drinkers compared to controls. This reduction was observed in absence of clinical manifestations of neuropathy, suggesting an underestimation of small fiber neuropathy (SFN) in AUD.[9] Only one study has analyzed the respective prevalence of large fiber neuropathy and small nerve fiber function using both nerve conduction studies and sensory threshold. The authors described, in a sample of 98 AUD patients, an exclusive small fiber loss of function (decrease thermal threshold) in 12.2%, an exclusive large fiber involvement in 20.4%, and both large and small fiber impairment in 25.5%.[5] Yet, the thermal abnormalities were determined in comparison to their own normative data from a control group, not further described. To date, there is no complete description of sensory profiles of patients suffering from AUD using the validated and standardized German Research Network on Neuropathic Pain (DFNS) QST protocol and their published normative data.

The present study aim was to assess pain intensity, potential neuropathic characteristics as well as any functional impact in patients with AUD undergoing withdrawal treatment. We also characterized the somatosensory profile using the DFNS QST protocol assessing functionality of small and large nerve sensitive fibers. A potential link between alcohol consumption, sensory profiles and reported pain was evaluated.

2 | METHODS

2.1 | Subjects

This observational monocentric cohort study, initiated by the Lausanne University Hospital pain center, was approved by the local ethics committee (CER-VD 2018-01138). Twenty-seven consecutive adult patients, hospitalized for alcohol withdrawal in the addiction Department were recruited during two periods: November 2018–January 2019 and October 2019–December 2019 (Figure 1). Patients were included at least 5 days after their voluntary admission in detoxification unit. All patients were considered, independently of their daily amount of alcohol intake. Exclusion criteria were other substance use disorders (except tobacco and cannabis) and a known condition possibly causing neuropathy (diabetes mellitus, HIV, cancer, thyroid dysfunction, nerve entrapment). All patients underwent a quantitative sensory testing (QST), a neurological examination and filled standardized questionnaires. An age and gender-matched healthy control group ($N = 13$) was prospectively recruited following completion of patient inclusion to undergo QST in the same experimental conditions as the patients (CERVD 2020-02259). Exclusion criteria for healthy

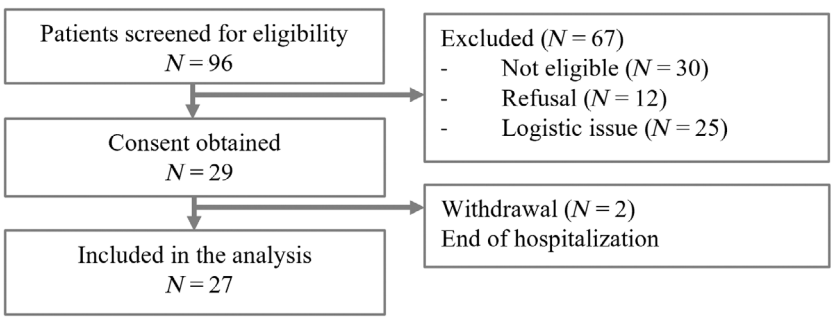


FIGURE 1 Flowchart illustrating the selection of study subjects.

controls were alcohol use disorder in addition to the same criteria as for patients.

2.2 | Alcohol consumption and dependence assessment

The alcohol dependence scale (ADS) was used to assess severity of alcohol dependence based on 25 items evaluating three factors: loss of behavioral control and heavy drinking; obsessive-compulsive drinking style; psychoperceptual and psychophysical withdrawal.[10]

The Lifetime Drinking History questionnaire (LDH) provided quantitative data on patterns of alcohol consumption.[11] This structured interview traced patient's alcohol consumption from the age of first regular drinking to the present within each major life phase. It assessed frequency of drinking, typical and maximum quantity consumed per occasion, types of beverage, style of drinking. The total lifetime dose of ethanol (TLDE) expressed in kg of ethanol/kg of body weight, alcohol use disorder duration defined as the number of years corresponding to the sum of alcohol intake periods were calculated. Since there was no minimal alcohol consumption defined in the inclusion criteria, the mean amount of alcohol intake over the two last years was calculated based on this questionnaire, in order to reflect recent alcohol consumption.

2.3 | Pain and psychological co-morbidities

Pain intensity and interference with daily life were assessed with the brief pain inventory (BPI).[12] Psychological comorbidities were evaluated using the hospital anxiety and depression scale (HADS),[13] pain coping through the pain catastrophizing scale (PCS)[14] and fear of movement through the TAMPA scale of kinesiophobia (TSK).[15] Quality of life was assessed through the World Health Organization Quality of Life Bref questionnaire, with raw scores converted into transformed domains scores ranging from 0 to 100 for physical health, psychological domain, social relationships, and environment (WHO-QOL, 1998).

2.4 | Neurological examination and questionnaires

The neurological examination, performed by a physician specialized in pain medicine, assessed walking on 6 parameters (speed, amplitude and regularity of gait, orientation, turn around, automatic arms swing, walking on a line), standing on 4 parameters (Romberg test eyes opened, eyes closed, finger-to-ground distance, posture), muscular strength on 6 parameters (Mingazzini and Barré test on lower limb, pronator drift test, upper limbs assessment (hand squeeze, finger abduction and adduction, elbow flexion and extension, arm internal/external rotation and abduction/adduction), lower limbs assessment (monopodal knee flexion, walking on heels and toes, knee/hip/foot extension and flexion), muscle tone), reflexes on 7 parameters (5 tendon reflexes (brachio-radialis, triceps, biceps, patellar, Achilles), plantar and abdominal reflexes), motor coordination on 2 parameters (finger-to-nose and heel-to-shin testing), tactile and proprioceptive sensitivity on 6 parameters (touch, position of the great toe, blind thumb grip, vibration sense wrist/ankle/toe, prick, cold) and cranial nerves on 10 parameters (voluntary and pursuit eye movement, pupillary reflexe, convergence reflexe, facial sensitivity, masseter contraction, facial motricity, swallowing/hoarseness, shoulder shrug/turn head to side against resistance, tongue movement). Clinical signs of neuropathy were assessed using the Neuropathy disability score (NDS)[16,17] and neuropathic symptoms using the « Douleur Neuropathique 4 ».[18] The Small Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN-SIQ) was collected.[19] The 13-items of this self-assessment tool investigate the two clinical presentations of small fiber neuropathy, that is, autonomic symptoms (changes in sweating pattern, diarrhea, constipation, urinary tract problems such as hesitancy and incontinence, dry eyes, dry mouth, orthostatism, palpitations, hot flushes) and sensory symptoms (sensitive leg skin, burning feet, sheet intolerance, and nocturnal restless legs). Each item is scored on a 4-point Likert scale (0-never present; 1-sometimes, 2-often, and 3-always present). The SFN-SIQ score is the sum of each item. There is no formally validated cut-off for this scale.

2.5 | Quantitative sensory testing

Quantitative sensory testing (QST) was performed according to the standardized protocol of the German Research Network Neuropathic Pain (DFNS)[20] by one experimenter (A.F.) on one hand and 1 foot, choosing the most affected side from patient's history.

The QST parameters were acquired in the following order: cold detection threshold (CDT), warm detection threshold (WDT), ability to detect temperature changes (thermal sensory limen, TSL), the number of paradoxical heat sensations during TSL (PHS), cold pain threshold (CPT), heat pain threshold (HPT) assessed using TSA II Peltier thermode (Medoc, Israel). Mechanical detection threshold (MDT) was assessed using Von Frey filaments, mechanical pain threshold (pin/prick thresholds, MPT) and mechanical pain sensitivity (MPS) were assessed using pinpricks, dynamic mechanical allodynia (DMA) using a brush, cotton wool and a Q-tip, wind-up ratio represents the pain summation to repetitive pinprick stimuli (WUR), pressure pain threshold (PPT) was assessed using a calibrated algometer (Wagner Instruments, USA), and vibration detection threshold (VDT) using a tuning fork.

After a log transformation of the raw data to follow a normal distribution, a z-score sensory profile was calculated using the formula: z-score = (value of the patient—mean value of published controls)/standard deviation of published controls). Negative z-scores indicate loss of function, and positive z-scores indicate a gain of function. For individual clinical assessment, each patient's QST values were compared with the corresponding age and gender reference values from the literature.[21] In addition to individual assessments, group comparisons were performed between AUD patients and an age- and gender- matched control group, locally recruited and tested in the same experimental conditions. This internal control was added to ensure the observed differences from the published controls could be attributed to patients' specificities and not differences in experimental setting.

TABLE 1 Description of the patient population: demographic data and scores of alcohol consumption, psychological health, and quality of life.

	N = 27	Mean	SD	% Above clinical cut-off
Demographic	21 ♂ (78%), 6 ♀ (22%) Age (year)	47.1	10.5	-
	BMI	25.6	4.8	4% (<19), 55% (>25)
	Nutrition score (abnormal if ≥3)	2.4	2.0	62.9%
	UPA (% Smokers)	19.7	16.6	97.5%
Alcohol consumption	Alcohol dependence Scale (ADS cut-off ≥9)	18.8	5.3	100%
	Nb years of regular consumption	30.0	10.4	-
	Nb day/month	19.0	6.5	-
	Nb drinks/day	10.0	7.6	-
	TLDE(kg ethanol/kg)	11.3	10.5	-
	Daily alcohol consumption last 2 years(g)	193.4	158.8	-
Mood disorder and quality of life	HADS Anxiety(% ≥8)	9.22	4.5	62.9%
	HADS depression (% ≥8)	4.7	3.7	18.5%
	QOL physical health	60.5	13.2	-
	QOL psychological	62.1	16.8	-
	QOL social relationships	56.3	18.6	-
	QOL environment	59	14.2	-

Abbreviations: HADS, hospital anxiety and depression scale; TLDE: total lifetime dose of ethanol; QOL: quality of life.

2.6 | Statistics

All the analyses were performed using SPSS Statistics 27 (IBM, Germany). For individual patients' QST analysis, Z scores above 1.96 (gain of function) or below −1.96 (loss of function) were considered as abnormal based on the DFNS methodology.[21] The *t*-test were performed to compare normally distributed z-scores between patients and the local control group for each modality. Bonferroni corrections for multiple comparisons were applied. Pearson correlations were calculated between BPI scores, thermal detection threshold and the total lifetime dose of ethanol (TLDE). Differences between patients with and without thermal hypoesthesia were evaluated by Chi-squares for gender and nutritional status and by *t*-test for TLDE and the mean daily intake over the last 2 years.

3 | RESULTS

3.1 | Demographic data and symptoms description

The patient demographic data are detailed in Table 1. All patients displayed clinical alcohol dependence according to ADS with signs of loss of behavioral control, obsessive-compulsive drinking style and withdrawal at different intensities: 5 patients with low dependence (ADS ≤ 13), 12 patients with intermediate dependence (14 ≤ NDS ≤ 21) and 10 patients with substantial dependence (22 ≤ NDS ≤ 30). The mean declared consumption was 10 drinks per day, 19 days per month, since 30 years with an important variability in the daily intake ranging from 3.5 to 39.3 daily drinks on average over the total period of consumption and from 2 to 56 drinks over the last 2 years. Mood and quality of life were altered (Table 1).

Pain was reported by 48% of the patients, yet with a very low mean pain intensity (1.0/10). Ten patients (37%) reported pain <3/10 and 3 patients (11%) reported pain comprised between 3 and 5/10. Pain interference with daily life was very low for most patients (mean 0.7/10) with 17 patients reporting no interference at all (63%) (Figure 2). Three patients reached clinical cut-off for pain catastrophizing and 15 for kinesiophobia (Figure 2). The duration of pain was variable: less than 3 months for 4 patients (15%), to 3 to 6 months for 3 patients (11%) and more than 3 years (6 patients, 22%). Among the 13 patients reporting pain, 50% complained from low back pain, 33% from pain in the extremities (hands or feet), 25% in the legs (including knees) and 17% in the cervical area/spine.

3.2 | Neurological examination

Eight patients (30%) had a fully normal neurological examination, 19 patients displayed abnormalities in their neurological exam (70%, see details in Table 2). The most frequent findings were areflexia and sensory loss. The Neuropathy Disability Scale (NDS) clinical examination revealed that 67% of patients had a no symptoms of neuropathy (NDS ≤ 2), 26% were considered having a mild neuropathy (3 ≤ NDS ≤ 5) and 7% a moderate neuropathy (NDS ≥ 6). According to the DN4 neuropathic pain detection tool, 18 patients had no symptoms of neuropathic pain (67%), 7 reported between 1 and 3 compatible manifestations (26%), and only 2 patients (7%) reached the clinical cut-off of 4 manifestations. The mean score for the small fiber detection tool SFN-SIQ was low (M = 3.4/39, SD = 4.1, no validated cut-off).

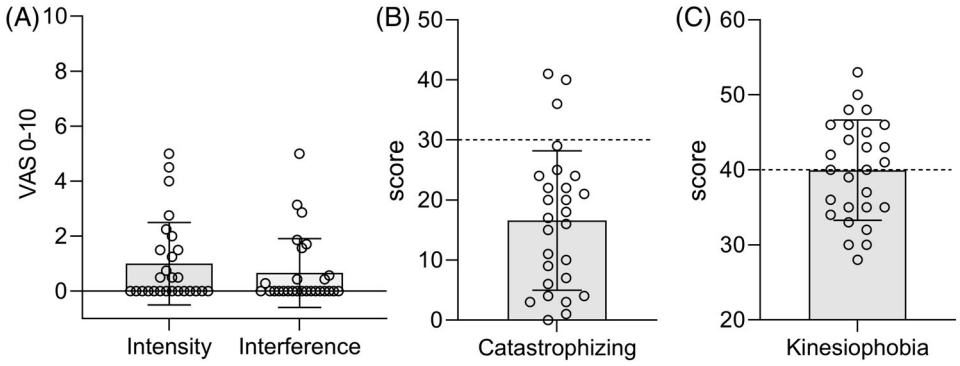


FIGURE 2 Pain characteristics and pain related scores. (A) Brief Pain Inventory with the intensity and interference sub-scales; (B) Pain catastrophizing scale; (C) Tampa scale of kinesiophobia. Each circle represents a patient suffering from AUD. The dotted line represents the clinical cut-off. Error bars represent standard deviations.

TABLE 2 Summary of the neurological examination findings in the 19 patients with at least one abnormal test.

Patient n°	Walking/6	Standing/4	Strength/6	Reflexes/7	Coordin./2	Sensitivity/6	Cranial n./10	Total
8	0	0	0	1	0	0	0	1
18	0	0	0	0	0	1	0	1
24	0	0	0	1	0	0	0	1
11	0	0	0	2	0	0	0	2
16	0	0	0	0	1	1	0	2
17	0	0	0	2	0	0	0	2
21	0	0	0	2	0	0	0	2
3	1	0	0	0	1	1	0	3
5	1	0	0	0	0	2	0	3
6	0	0	0	1	0	2	0	3
9	0	0	0	3	0	0	0	3
10	0	0	0	2	0	1	0	3
23	1	0	0	1	0	1	0	3
25	0	0	0	3	0	0	0	3
4	0	0	0	4	0	0	0	4
26	0	0	0	2	1	1	0	4
7	1	0	0	5	0	0	0	6
27	1	0	0	3	0	1	1	6
14	0	1	2	3	2	2	0	10

Note: The patients (ID in first column) are organized in the ascending order of abnormal tests (total *N* of abnormal tests, last column). The number of abnormal results is presented for each domain in a separate column: walking on 6 parameters (speed, amplitude, orientation, turn around, automatic arms swing, walking on a line), standing on 4 parameters (Romberg test eyes opened, eyes closed, finger-to-ground distance, posture, muscular strength (6 parameters), reflexes (7 parameters), motor coordination (2 parameters), sensitivity (tactile and proprioceptive, 6 parameters), cranial nerves (10 parameters) with a color gradient from green (=normal) to dark orange (=4 or more abnormal tests).

3.3 | Quantitative sensory testing

The individual sensory profiles of patients are represented in Figure 3A,B. Sensory loss of function of small fibers (i.e. any decrease in thermal detection: CDT, WDT or TSL on either hand or foot) was observed in 14/27 patients (52%) when compared to published normative data.[21] To provide more details: 19% of all patients displayed thermal hypoesthesia on the hand for cold, 26% for warm and a 19% a hypodetection of temperature changes. Thermal hypoesthesia was less frequent for the foot (4% for cold and warm and 7% for temperature change). When compared to local age/gender matched controls, patients had a significant decrease in light touch detection (MDT) on the hand (Figure 3, panel C and D) and no significant differences in sensory profile for the foot.

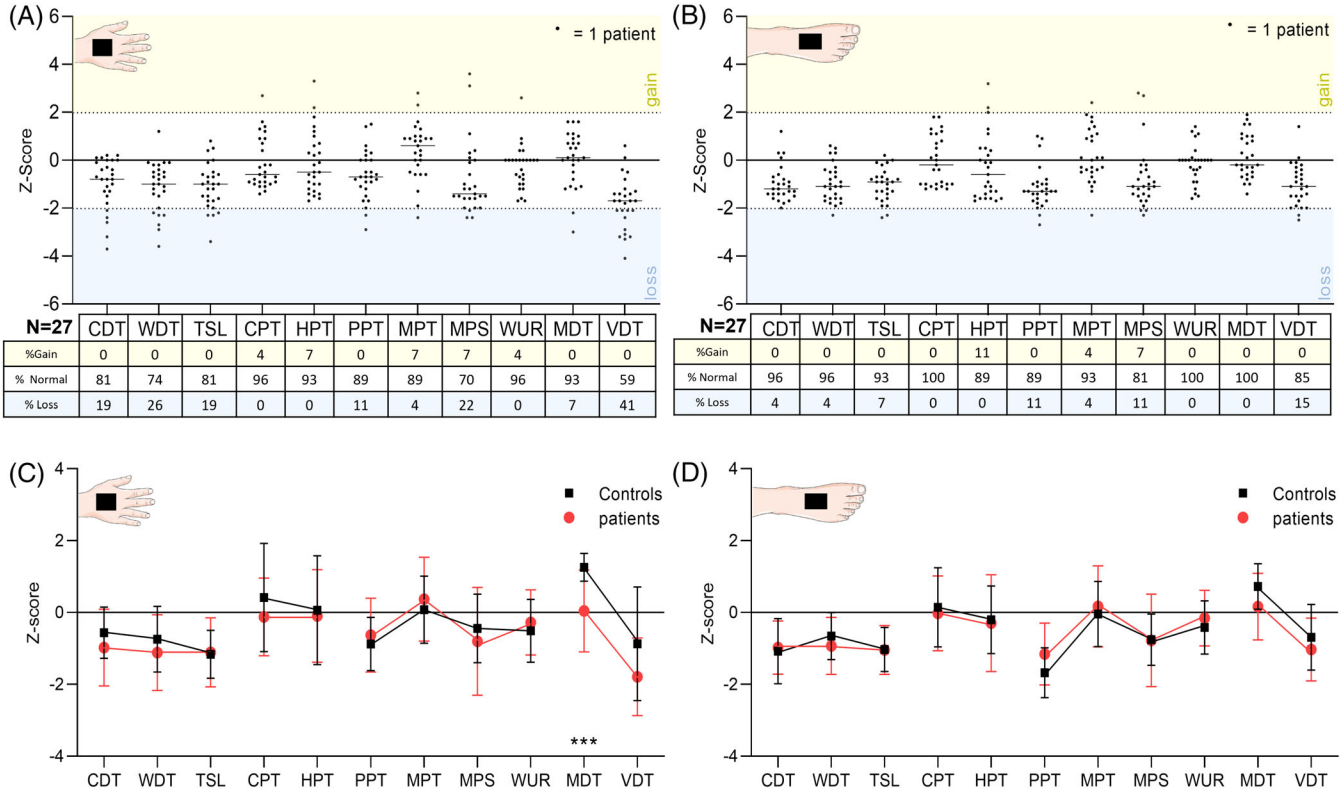
3.4 | Categorization of patients based on correlates of small and large fiber function

Based on the Neuropathy Disability Scale as a measure of large fibers alterations and on the presence of thermal hypoesthesia upon QST to determine small fiber alterations, 33% had exclusively small fiber impairment, 15% exclusively large fibers impairment and 19% both large and small fiber impairment, 33% of patients had a fully normal profile.

3.5 | Correlations between alcohol consumption, pain and sensory profile

There were no significant correlations between BPI pain scores, thermal detection thresholds and TLDE. There were no significant differences in alcohol consumption, dependence or sensory profile between patients reporting pain or not.

Patients with thermal hypoesthesia during QST (i.e., with signs of small nerve fibers loss of function) were compared to those without (Figure 4), showing no significant difference in terms of age, gender nor



N=27	CDT	WDT	TSL	CPT	HPT	PPT	MPT	MPS	WUR	MDT	VDT
%Gain	0	0	0	4	7	0	7	7	4	0	0
% Normal	81	74	81	96	93	89	89	70	96	93	59
% Loss	19	26	19	0	0	11	4	22	0	7	41

N=27	CDT	WDT	TSL	CPT	HPT	PPT	MPT	MPS	WUR	MDT	VDT
%Gain	0	0	0	0	11	0	4	7	0	0	0
% Normal	96	96	93	100	89	89	93	81	100	100	85
% Loss	4	4	7	0	0	11	4	11	0	0	15

FIGURE 3 Quantitative Sensory Testing profiles assessed on the most affected hand (A, C) and foot (B, D). Patients' individual results are presented on the upper panels (A, B). Z-score beyond 1.96 (in the yellow band) correspond to a sensory gain of function and below −1.96 (in the blue band) to a loss of function, in comparison to published normative data. The distribution between gain, loss or normal sensory function are presented for each 7modality in the tables below panels A and B. Group comparison between patients and the local controls group are presented in the lower panels (C, D). Cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), cold pain threshold (CPT), heat pain threshold (HPT), pressure pain threshold (PPT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), wind-up ratio (WUR), mechanical detection threshold (MDT), vibration detection threshold (VDT).

(A)

	Gender		Age	Nutritional status		Total Lifetime Dose of Ethanol (kg_{OH}/kg_{Bw})
	♂	♀		Norm.	Abno.	
Thermal hypoesthesia (n= 14)	12	2	44.3 ± 9.6	n=5	n=9	11.7 ± 11.6
No thermal hypoesthesia (n=13)	9	4	50.2 ± 10.7	n=5	n=8	11.0 ± 9.7

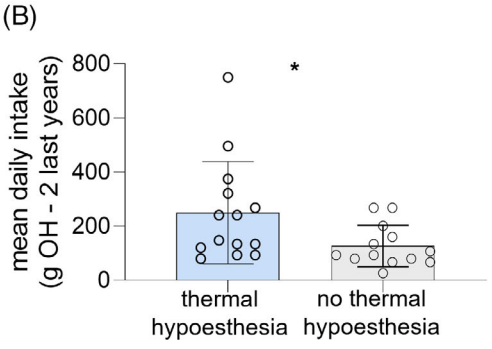


FIGURE 4 Comparison of potential contributors to alcohol-related peripheral neuropathy between patients with (blue) and without (grey) thermal hypoesthesia upon QST reflecting a loss of function of small nerve fibers. This figure depicts the data of gender, nutritional status, total lifetime dose of ethanol (panel A) and mean daily intake over the last 2 years (panel B). *$p < .05$.

nutritional status. Patients with thermal hypoesthesia did not report a larger life-time alcohol consumption (TLDE) ($t(25) = 0.1$, $p = .9$) (Figure 4A), however they reported a significantly higher mean daily intake of ethanol over the last 2 years (mean = 9 more daily drinks) than patients without thermal hypoesthesia ($t(25) = 2.2$, $p = .04$) (Figure 4B).

4 | DISCUSSION

This cross-sectional study of 27 consecutive patients suffering from alcohol use disorders undergoing withdrawal treatment revealed that half of the patients reported pain. Yet pain intensity was weak, leading to a low interference with daily life, and the characteristics did not support a neuropathic component in all but two patients. This study is the first report of a functional impairment of small nerve fibers using standardized quantitative sensory testing performed according to the DFNS protocol in AUD patients with thermal hypoesthesia observed in 52% of the patients.

In studies focusing on alcohol-related peripheral neuropathies, pain prevalence varies between 28% and 75% with a pooled prevalence of 42% (CI 29%–56%, $n = 325$).[7] Yet most of the studies in this AUD population considered pain as a dichotomous factor (present or absent) without any further information about pain duration, intensity or characteristics.[22]

To our knowledge, only one American study described pain severity and characteristics in $N = 451$ treatment-seeking AUD patients.[23] They described that 58% of the patients reported recurrent pain (at least 1 day per week). This ratio is comparable with the one observed in our sample (52%), yet higher than in the general population (20%).[24,25] Furthermore, among AUD patients experiencing pain, the mean pain intensity was 5/10 with 58% of the patients reporting back pain, 35% neck pain and 34% headaches.[23] In our cohort, the mean intensity was lower (2.1/10) but back pain was also a predominant presentation, as is the case in the general population.[26]

Surprisingly, the proportion of patients with neuropathic pain characteristics was low (7% in our cohort). This rate contrasts with what is often introduced in research articles, with pain being presented as the main symptom of alcohol related-peripheral neuropathy.[27] This low proportion of neuropathic pain in our sample could be due to the selection process of patients. In our study, we included consecutive patients suffering from AUD, regardless of the presence of pain or neuropathic symptoms as well as their level of alcohol consumption. We could hypothesize that painful neuropathy is a more severe form, presenting at a later stage of disease or in a subset of patients. We found no information in the literature linking the severity of an alcohol-related neuropathy (intensity of symptoms, distal or proximal alterations, number of clinical signs) to the presence of pain nor to an eventual functional impact. In our study, there were no differences in sensory profiles and scores of neuropathy between patients reporting pain or not. In a large cohort ($N = 350$) of mixed etiology polyneuropathies,[28] QST profiles did not significantly differ between a group with and without pain. Nevertheless, in diabetic peripheral neuropathy, the presence and the intensity of neuropathic pain is associated with a greater severity of the neuropathy.[29,30] A potential link between alcohol-related neuropathy and the severity of neuropathic pain deserve further investigations with multiple investigation techniques in large samples of patients with more pain symptoms.

Bidirectional associations between AUD and chronic pain in general have been reported.[31] The present study focused on chronic pain secondary to alcohol exposure in AUD patients. However, many patients use alcohol to alleviate pre-existing or concomitant chronic pain.[32,33] Nevertheless, alcohol consumption in this context can induce adverse consequences such as increased pain sensitivity[31,34,35] hence reinforcing this vicious circle. Because pain can be a significant risk factor for drinking relapses, it could prevent alcohol detoxification treatments and recovery,[36] there is an urgent need to better identify and manage pain (neuropathic or not) in these patients.[23,37] An integrated treatment incorporating both pain management and relapse prevention was shown to be effective in a small sample of patients with concurrent chronic pain and AUD.[38]

The quantitative sensory testing (QST) revealed a sensory loss of function of small fibers (i.e., any decrease in thermal detection) in 52% of AUD patients while prior work[5] reported abnormal thermal detection only in 38%. These authors used a different QST methodology and compared patient's thresholds to their own control group. When compared to our local control group, no significant differences were revealed, potentially due to the small sample size. Hence, we focus our conclusion on the individual data. To our knowledge, we present the first report of functional assessment in AUD using the DFNS protocol[20] and the published reference values [21]. QST as a method of SFN detection has been previously examined in a mixed sample of 149 patients with a sensitivity of 85.1% and specificity of 80.8% when using both limit and level methods. Yet only foot thermal parameters were considered and the sensitivity/specificity of QST for other body locations still need to be established. Hence, in our study, we provided a descriptive analysis of the sensory profile, performed on both hand and foot and therefore these results must be interpreted with caution since there is no intention to diagnose SFN. QST as a psychophysical test is inherently subjective with some bias in the comparison to the normative data and therefore a combination with a clinical evaluation and an objective measure of intraepidermal nerve fiber density is recommended for the diagnosis.[39–41] Clinically, the biopsy is recommended for symptomatic patients. Hence, ethically, such an invasive procedure was not justified in our observational study.

Skin or nerve biopsies studies looking at small nerve fibers reported a decreased density in AUD compared to controls but did not report on the percentage of patients presenting such a decrease nor the impact on small fiber function.[8,9,42]

The symptom-based detection scores (both autonomic and sensory) for small fiber neuropathy was low in our cohort using the SFN-SIQ. Even if there is no standard clinical cut-off, a value of 5 had a sensitivity of 80% and a specificity of 81.8% to detect symptoms in patients with either SFN or mixed fibers damage ($N = 55$).[43]

Using that cut-off, only 8 patients (30%) had significant symptoms of small fiber neuropathy.

Based on the NDS, 33% of patients tested in our study displayed sign of large fiber peripheral neuropathy. In a meta-analysis of the prevalence of large fiber peripheral neuropathy in AUD, using history and clinical examination, the pooled estimate was 44% (CI 36%–53%; $n = 2590$) (Julian et al., 2019). This rate was even higher when the diagnosis of peripheral neuropathy was based on nerve conduction studies (46%; CI 36%–57%; $n = 1596$), suggesting a large number of silent cases. Differences in prevalence of large fiber neuropathy between samples could be explained by a selection bias. Since we did not set a minimal daily alcohol intake in our study contrary to several others,[4,44] the median consumption was lower (136 g/per day) with 10 patients in our sample (37%) not reaching a frequently used inclusion cut-off of 100 g per day.

As with SFN, asymptomatic presentations are frequent for large fiber peripheral neuropathy. None of our patients spontaneously complained of neuropathic symptoms, as previously reported in another study where 85% of mild neuropathy, 60% or moderate and 33% of severe polyneuropathy were asymptomatic.[6]

A selective small fiber functional impairment without large fiber implication has been described in 33% of our patients. Nevertheless, this rate could be overestimated since asymptomatic large fiber impairment was not considered, in absence of nerve conduction study. A prior study reported 12% of selective small fiber impairment,[5] whereas other research reported both small and large fiber loss with variable predominance[4,8,9,42,45]; A study using sural nerve biopsies found that patients with a shorter history of AUD disease had predominantly small fiber loss compared to those with a longer disease duration who had more large fiber involvement.[8] In our cohort, there was no difference in disease duration nor in age between patients with an exclusive small fiber impairment and those with large fiber impairment, not providing further support to this interesting hypothesis. A longitudinal study assessing both small and large fibers across time would provide more valuable information on a potential temporal evolution from small fiber to large fiber neuropathy in AUD.

While there is evidence for peripheral neuropathy specifically associated with thiamine deficiency, most studies in alcoholic neuropathy do not report correlations with markers of nutritional status.[8,46] Available data suggest that the pathophysiology of thiamine-deficiency-related and alcoholism-related neuropathy are different.[4,27] In our study, the lack of difference between patients according to their nutritional status did not support this nutritional deficit hypothesis either, although, given the size of our sample, this needs to be interpreted with caution.

Concerning a direct toxic effect, several studies reported a link between alcohol consumption (disease duration, alcohol intake, drinking pattern) and incidence of neuropathy.[7] The most frequently reported risk factor is TLDE[44,46–50] with an inverse correlation between TLDE and sural nerve amplitude.[6] In our study, TLDE was not correlated with neuropathy severity (neither NDS nor thermal thresholds) as reported also in other prior studies.[5,51] Several hypotheses could explain these inconsistent results. First, there is no standard to define alcohol related peripheral neuropathy with some research relying on nerve conduction studies, others on nerve biopsies and/or clinical assessment. Moreover, as already mentioned most of the studies set a minimal intake of 8 daily drinks (or 100 g of ethanol) during 2 years for patient inclusion or simply reported such an intake in their population. The fact that 37% of our patients would not have reached this threshold could explain this lack of correlation in our cohort.

However, we observed that patients with impaired small fiber function reported a higher daily intake (twice the dose in mean) over the last 2 years compared to patients without hypoesthesia, suggesting an impact of the recent dose of alcohol intake on small fibers function.

Alcohol-related signs of neuropathy are common and mostly asymptomatic in patients with alcohol use disorders. Patients with a higher alcohol consumption over the last 2 years showed a greater impairment of small fiber function. We found a high prevalence of pain of any origin, but it is however unlikely to be caused by peripheral neuropathy given the non-length-dependent distribution and the absence of neuropathic pain features.

Chronic pain in AUD therefore deserves to be better evaluated and managed as it represents a potential opportunity to improve long-term clinical outcomes, potentially participating to relapse prevention. Small fiber neuropathy in AUD is still under-investigated, therefore warranting future studies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Zenodo at https://zenodo.org/record/7783973, reference number 10.5281/zenodo.7783973.

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