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Classification of the Pain Nature of CRPS Type 1, Based on Patient complaints, into Neuropathic Pain and Nociceptive/Inflammatory Pain, Using the McGill Pain Questionnaire

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Abstract

Objectives: The precise causes of Complex Regional Pain Syndrome (CRPS) are as yet not well known. Some consider CRPS type 1 without apparent nerve injury to arise due to a prolonged inflammatory state after initial trauma and its underlying pathophysiology indicates Nociceptive/Inflammatory Pain (NocP) components. Yet others have shown clear direct evidence of nerve injury in CRPS type 1-affected limbs, and they consider CRPS type 1to be Neuropathic Pain (NeP). The McGill Pain Questionnaire (MPQ) has the potential to diagnose pain disorders as well as suggest the underlying pathophysiology.

Methods: We investigated pain characteristics of 165 NeP and 66 NocP patients, by using the 78 words of the MPQ, and thereby developed a discriminant function which efficiently discriminates NocP from NeP. We then applied this function to 36 CRPS type 1 patients' complaints and classified their pain into either NocP or NeP.

Results: The discriminant probability of the function was 81.0% (chi-square, p=0.24) and this function revealed 47.2% of CRPS type 1 patients' complaints were classified as NocP and 52.8% as NeP. These subgroups showed almost comparable demographic data.

Considerations: Our results indicate that CRPS type 1 cannot be classified as NeP or NocP dichotomously according to pain descriptions. This raises the possibility that CRPS type 1 represents a "mixed" pain mechanism comprised of both NeP and NocP.

Introduction

Pain is inherently subjective. To understand another people's pai, we must accurately interpret what others say or show by their behaviors. In many investigations of pain, various measurements and questionnaires are used to evaluate pain as objectively as possible. Among these, the McGill Pain Questionnaire (MPQ) is one of the most widely-used and well-validated questionnaires [1]. The MPQ consists of 78 pain descriptors, which are classified into 20 sub-groups. Furthermore, the 20 sub-groups can be scored and assessed in view of four major dimensions of pain: sensory, affective, evaluative and miscellaneous pain. Some investigations have suggested that the MPQ is clinically useful for diagnosing the pain complaints of patients on the basis of the nature of their pain descriptions [2-4]. Patients with certain pain syndromes frequently select characteristic words in the MPQ to describe their pain. For example, cancer pain patients consistently characterize their pain as shooting, sharp, gnawing, burning and heavy, while those with neuropathic pain tend to describe theirs as burning, shooting, tingling, piercing, and so on [1,5,6].We previously succeeded in demonstrating two categories of neuropathic pain [one involves superficial-pain descriptions (e.g., burning, tingling, piercing and so on), and the other deep-somatic descriptions (e.g., squeezing, cramp-like, twisting and so on)] which are differently alleviated according to mirror visual feedback treatment [7]. Thus, the nature of pain is useful for suggesting underlying the pathophysiological mechanism(s), and the MPQ has the potential to diagnose pain disorders and reveal the causative pathophysiology.

Following a noxious event, Complex Regional Pain Syndrome (CRPS) may occur accompanied by severe pain disproportionate to the initiating event, edema, skin color asymmetry, skin temperature asymmetry, atrophic changes and motor functional limitations. The precise cause of CRPS is as yet not well known, though it is clear that CRPS often induces a number of functionally debilitating effects on daily life. CRPS is classified into CRPS type 1, previously known as reflex sympathetic dystrophy without apparent nerve injury, and CRPS type 2, previously known as causalgia with apparent nerve injury. Although the symptomatology between CRPS type 1 and type 2 is known to be similar, the etiologies of respective types of CRPS are considered to be different according to presence or not of an overt nerve injury. CRPS type 2 is generally considered to be one of forms of neuropathic pain, on the basis of re-definition and the diagnostic flow-chart of neuropathic pain proposed by the Neuropathic Pain Special-Interest-Group of the International Association for the Study of Pain (IASP) [8]. On the other hand, CRPS type 1 is not included within the neuropathic pain category because the diagnosis of CRPS

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type 1 is clinically made by absence of documented nerve lesion. What is the underlying pathophysiological mechanism(s) of CRPS type 1? Some researchers have suggested that CRPS type 1 develops due to prolonged inflammation following a traumatic event and they propose that CRPS type 1 is a nociceptive/inflammatory form of pain. Clinically, understanding the pathophysiological mechanism(s) underlying pain is critical to selecting optimal treatment strategies, especially pharmacotherapy. In the present study, we aimed to elucidate whether the etiology of CRPS type 1 is nociceptive or neuropathic according to pain quality descriptors of the patients. We initially examined the discriminant validity of the classification by providing a list of distinct pain quality descriptors in the MPQ to dichotomize pain as nociceptive or neuropathic. Next, we classified pain descriptions given by patients with CRPS type 1 into nociceptive or neuropathic pain by using the MPQ.

Methods

Experiment 1

Subjects: Two hundred thirty-one patients, referred to Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital and the Center for Pain Management (Anesthesiology) at Osaka University Medical Hospital during the period from July 2003 to January 2008, participated in this study. The inclusion criteria were: (1) suspicion (by the referring physician) of neuropathic pain and nociceptive/inflammatory pain in the extremities; (2) mean pain intensity in the past month (recorded at inclusion) >1 on an eleven-point numerical rating scale (NRS) (0=no pain, 10=worst possible pain); (3) pain duration >3 months; and (4) age >18 years. The exclusion criteria were: (1) comorbid psychiatric disorders like as schizophrenia, major depression, character disorders or other psychotic conditions according to the ICD-10 criteria and (2) inability to answer pencil-and-paper questionnaires by themselves. The enrolled patients were then divided into two groups: neuropathic pain (NeP, n=165) and nociceptive pain (NocP, n=66).The latter includes inflammatory pain as assessed by experienced pain physicians on the basis of history, local pain distribution and clinical examinations in addition to certain imaging studies. Criteria for NeP group assignment were based on those for diagnosis as redefined by the IASP Neuropathic Pain Special-Interest-Group, by experienced pain physicians: pain distribution neuroanatomically plausible, history suggesting relevant nerve lesion, negative (e.g., hypoesthesia) or positive (e.g., hyperalgesia) sensory signs confined to innervation territory of the lesioned nervous structure, and diagnostic imaging or electrophysiological tests confirming the nerve lesion [8]. CRPS type 2 patients were categorized into the NeP group. By contrast, CRPS type 1 patients were included in neither NeP nor NocP in Experiment 1. The NocP group included patients with orthopedic joint degenerative diseases or post-traumatic chronic pain syndromes involving the extremities who did not meet the criteria for CRPS type 1 in the Japanese population [9]. Patients were enrolled after providing informed consent. The study was approved by the Local Ethics Committees and adhered to the Helsinki Declaration. Demographic data were shown in Table 1.

Discriminant function analysis of pain descriptions: The MPQ, Hospital Anxiety and Depression (HAD) rating scale and the Pain Disability Assessment Scale (PDAS) were all carried out when the participants were referred to our hospital for the first time, and the data were collected. From a list of pain descriptors (78 words) in the MPQ Japanese version, the patients were asked to choose one or no descriptor, which best described their pain, from the aforementioned 20 sub-groups in a pencil-and-paper manner by themselves [10].

	NocP	NeP
N	66	165
Age (years)	47.4 ± 18.3	62.8 ± 14.3
Gender (female)	41	76
Pain duration (month)	21.3 ± 53.8	31.8 ± 45.2
NRS (pain intensity)	5.5 ± 2.5	6.6 ± 2.4
MPQ total score	22.1 ± 16.7	20.4 ± 15.6
HAD score Anxiety	8.8 ± 4.5	8.9 ± 4.9
HAD score Depression	8.9 ± 5.1	9.2 ± 5.2
PDAS score	26.7 ± 13.5	29.3 ± 16.5

Table 1: Demographic data of 231 participants.

Numerical values indicate means ± SD. Statistical analyses were performed using the Mann-Whitney test. NocP indicates nociceptive pain; NeP indicates neuropathic pain; NRS indicates numerical rating scale of pain intensity.

	CRPS type 1	NocP subgroup	NeP subgroup	*Pvalue*
N	36	17	19	-
Age (years)	48.1 ± 16.9	51.9 ± 15.2	44.7 ± 18.0	*0.21*
Gender (female)	22	9	13	*<0.01*
Pain duration (month)	441.0 ± 234.0	378.9 ± 248.3	496.6 ± 211.4	*0.72*
NRS (pain intensity)	6.4 ± 1.8	6.2 ± 1.6	6.5 ± 2.8	*0.64*
MPQ total score	21.5 ± 14.2	22.9 ± 14.8	20.2 ± 13.9	*0.58*
HAD score Anxiety	8.6 ± 4.1	8.0 ± 4.2	9.2 ± 4.2	*0.43*
HAD score Depression	9.6 ± 5.8	11.3 ± 7.0	8.2 ± 4.2	*0.15*
PDAS score	26.0 ± 14.3	27.9 ± 15.1	24.4 ± 13.9	*0.50*

Table 2: Demographic data of 36 CRPS type 1 patients, 19 neuropathic pain and 17 nociceptive pain subgroups.

CRPS type 1 patients were divided into neuropathic pain and nociceptive pain subgroups on the basis of the discriminant function which is obtained in Experiment 1. Numerical values indicate means ± SD. Statistical analyses were performed using the Mann-Whitney test.NocP indicates nociceptive pain; NeP indicates neuropathic pain; NRS indicates numerical rating scale of pain intensity.

The discriminant function analysis is similar to a regression analysis. The discriminant function analysis builds a predictive model for group membership, and the model is composed of a discriminant function based on linear combinations of predictor variables. The discriminant function analysis assesses how well the independent variables separate the groups: the analysis defines a coefficient of each independent variable. A discriminant score can be calculated based on the weighted combination of the independent variables. In the present study, we used the discriminant function analysis to define a coefficient of each descriptor in the MPQ and maximize the difference between the discriminant scores in NocP and NeP groups. The resultant discriminant function was applied to NocP and NeP groups and then we evaluate the probability for whole of the participants and respective groups. By applying this function to each patient's MPQ responses, we were able to classify the responses as NeP, if the numerical value of the discriminant function was >1, or NocP if it was <1.The chi-square test was used to validate the robustness of the discriminant function. Significance was accepted at the 5% level. Each analysis was performed using Dr. SPSS (Statistical Package for the Social Sciences, USA).

Experiment 2

Subjects: The study was also approved by the Local Ethics Committees and adhered to the Helsinki Declaration.

Thirty-six CRPS type 1 patients (age, 48.1 ± 16.9 years; pain duration, 21.4 ± 20.7 months; female, 21; affected limb, upper 11, lower 14, both 2; affected side, left 20, right 13, both 3; NRS, 6.4 ± 1.8; HAD

anxiety 8.6 ± 4.2, depression 9.6 ± 5.8; PDAS 26.0 ± 14.3), referred to the two hospitals during the period from July 2003 to January 2008, were eligible for participation in this study (Table 2). All met the Japanese diagnostic criteria for CRPS, but did not have any apparent nerve injuries which are evaluated by experienced pain physicians. The patients answered the same set of pencil-and-paper questionnaires (the MPQ and so on) by themselves. The patients were enrolled after providing informed consent.

Discrimination of descriptions of CRPS type 1, by applying the discriminant function between neuropathic pain and nociceptive pain: On the basis of the discriminant function developed in Experiment 1, CRPS type 1 patients' responses to the MPQ were classified as NeP or NocP. Then, we compared demographic data of the NeP and NocP subgroups in CRPS type 1 patients by using the Mann-Whitney test and the chi-square test.

Results

Experiment 1

Coefficients for pain descriptors in the MPQ and discriminant probability

The distribution of pain descriptors chosen from the list of the MPQ and coefficients for each pain descriptor to classify pain as NocP or NeP dichotomously are shown in Table 3. We set the coefficients for each word and the constant term, to discriminate the two groups most efficiently, by using the discriminant function analysis. Among 78 pain descriptors, "annoying" and "tearing" were discarded: their coefficient was set as 0. On the other hand, "gnawing", "smarting" and "frightful" were characterized as neuropathic descriptions because their coefficients were more than 3. "Cruel" and "troublesome" were characterized as nociceptive/inflammatory descriptions but their contribution to categorize patients' pain response to the MPQ into NocP was relatively small because their absolute value of coefficient is around 1.6 at most.

The probability of this discriminant function was 81.0%

Group	Sub-group	Descriptor	Coefficients
1 sensory	1 temporal	flickering	1.12
		quivering	0.18
		pulsing	-0.20
		throbbing	1.20
		beating	0.44
		pounding	-1.32
	2 spatial	jumping	0.70
		flashing	0.41
		shooting	0.51
	3 punctate pressure	pricking	0.00
		boring	1.62
		drilling	-0.37
		stabbing	1.30
		lancinating	0.23
	4 inciseve pressure	sharp	-0.47
		cutting	1.28
		lacerating	-0.41
	5 constructive pressure	pinching	-1.44
		pressing	-0.34
		gnawing	3.62
		cramping	-0.30
		crushing	0.17
	6 traction pressure	tugging	0.83
		pulling	1.24
		wrenching	-0.56
	7 thermal	hot	0.13
		burning	0.27
		scalding	0.00
		searing	2.94
	8 brightness	tingling	-1.10
		Itchy	-0.79
		smarting	3.41
		stinging	-0.55
	9 dullness	dull	0.34
		sore	1.30
		hurting	-0.77
		aching	1.05
		heavy	0.95
	10 sensory miscellaneous 1	tender	-0.34
		taut	0.68
		rasping	1.13
		splitting	-0.62
2 effective	11 tension	tiring	-0.94
		exhausting	0.37
	12 Autonomic	sickening	-0.84
		suffocating	-0.76
	13 fear	fearful	-0.63
		frightful	3.14
		terrifying	0.16
	14 punishment	punishing	-0.27
		grueling	-0.29
		cruel	-1.64
		vicious	1.30
		killing	0.88
	15 affective miscellaneous	wretched	0.41
		blinding	0.16
3 evaluative	16 evaluative	annoying	0.00
		troublesome	-1.57
		miserable	0.07
		intense	-1.07
		unbearable	-1.83
4 sensory miscellaneous 2	17 sensory miscellaneous 2	spreading	0.19
		radiating	0.93
		penetrating	-1.07
		piercing	-0.50
	18 sensory miscellaneous 2	tight	0.86
		numb	-0.14
		drawing	-1.17
		squeezing	-1.1
		tearing	0.00
	19 sensory	cool	0.35
		cold	0.25
		freezing	0.
5 affective miscellaneous	20 affective-evaluative miscellaneous	nagging	-0.24
		nauseating	0.94
		agonizing	0.05
		dreadful	1.35
		torturing	0.07
		Constant term	-0.49

Table 3: Coefficients for 58 pain descriptors in the MPQ and a constant term in the discriminant function between neuropathic pain and nociceptive pain.

(Wilks'slambda, 0.64; chi-square test, p=0.24). The probabilities of the function for NocP and NeP were 80.3% and 81.2%, respectively.

Experiment 2

CRPS type 1 patient's complaints of their pain characteristics

Applying the discriminant function developed in Experiment 1, 19 CRPS type 1 patients' descriptions based on the MPQ were classified into NocP (47.2%) and 17 were classified into NeP (52.8%). Demographic data of NocP and NeP subgroups of CRPS type 1 patients were almost similar, except for gender (Table 2).

Discussion

Pathophysiological mechanisms underlying CRPS type 1 are as yet poorly understood. Some researchers have suggested that CRPS type 1 is nociceptive and inflammatory pain, based on the following concepts and observations: the axonal reflex and retrograde secretion of neurotransmitters from peripheral nerve endings into peripheral tissues can induce dilation and hyper permeability of small vessels, resulting in skin erythema, edema and temperature elevation, and peripheral nerve sensitization results in allodynia, hyperalgesia and severe pain inappropriate to the initiating event [11]. Furthermore, pro-inflammatory cytokines, mainly Tumor Necrosis Factor alpha (TNF-alpha) and Interleukin-6 (IL-6), are reportedly elevated in CRPS-affected limbs but not in CRPS-unaffected limbs [12]. On the other hand, other researchers have suggested that CRPS type 1 is neuropathic pain based on direct evidence of nerve injury. Oaklander et al. demonstrated loss of axons in the CRPS-affected limb by means of skin biopsy, indicating hypoesthesia of CRPS-affected limbs; and Blaes et al. reported autoantibodies to the surface of peripheral autonomic neurons in sera from CRPS type 1 patients, which produced sympathetic dysfunction in CRPS-affected limbs [13,14]. Thus, the controversy as to whether CRPS type 1 is primarily neuropathic or nociceptive has raged for more than two decades. Clinically, understanding the underlying pathophysiological mechanism(s) of pain is critical to selecting appropriate treatment strategies, especially pharmacotherapy. However, in human pain patients, it is very difficult and often impossible to define the mechanism(s). Instead, we usually infer the mechanism(s) from characteristic pain descriptions, in combination with physical and imaging examinations. One of the most exciting features of the MPQ is its potential value as an aid in the differential diagnosis of various pain syndromes [1]. To support this critical understanding in clinical settings, we developed a discriminant function based on MPQ descriptions and found that moderate probability could be demonstrated. In the present study, by applying the discriminant function to pain descriptions of CRPS type 1, we classified about a half of our CRPS type 1 patients as NocP and the other half asNeP. Therefore, our findings suggest that the underlying pathophysiological mechanism(s) of CRPS type 1 is in a gray zone between NeP and NocP. Recently. The mixed pain condition has been proposed to be the pathophysiological mechanism underlying chronic pain in clinical settings. With a prolonged nociceptive and inflammatory state, for example, neuronal hyper-excitability can occur in the spinal dorsal horn. Neuronal hyper-excitability is also observed with NeP. Furthermore, the actions of inflammatory mediators originating from peripheral tissue and proliferation of lymphocytes in peripheral nerves can induce neuronal inflammation and inflammatory-neuropathic pain [15]. Supporting evidence comes from Freynhagen et al. study showing that chronic low back pain, which has been considered to be due to mechanical and inflammatory nociception, includes a neuropathic component as revealed by using a neuropathic pain screening tool [16]. Thus, based on such observations, the participation of nociceptive as well as neuropathic mechanisms has been confirmed in chronic pain states, and is thus proposed to be a mixed pain condition [17]. In the present study, the discriminant function apparently showed moderately-high probability (more than 80%). However, the function was not sufficiently robust nor was the results statistically significant. This might be due to ambiguity caused by NeP and NocP group participants in Experiment 1 having both neuropathic and nociceptive components, namely mixed pain. Considering that a cohort of CRPS type 1 patients would have both neuropathic and nociceptive mechanisms and CRPS type 1 might well be a mixed pain disorder, it would be not be surprising for CRPS type 1 to be dichotomously classifiable as neither NeP nor NocP based on such an ambiguous function. Our findings would be helpful to select optimal treatment strategies for CRPS type 1.

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