Acta Neurol Scand 2004: 110: 368–376 DOI: 10.1111/j.1600-0404.2004.00341.x
Printed in UK. All rights reserved

ACTA NEUROLOGICA
SCANDINAVICA

Spectrum of cutaneous hyperalgesias/ allodynias in neuropathic pain patients

Verdugo RJ, Bell LA, Campero M, Salvat F, Tripplett B, Sonnad J, Ochoa JL. Spectrum of cutaneous hyperalgesias/allodynias in neuropathic pain patients.
Acta Neurol Scand 2004: 110: 368–376. © Blackwell Munksgaard 2004.

Objectives – The aim of this study was to discern the pathophysiological bases for neuropathic hyperalgesias. *Methods* – In this study, neurological and neurophysiological evaluation of 132 consecutive hyperalgesia patients using rigorous clinical and laboratory protocols were carried out. *Results* – Two discrete semeiologic entities emerged: classic neurological vs atypical, fulfilling taxonomically complex regional pain syndrome (CRPS) II and I, respectively. The classic group (34.9%) exhibited sensorimotor patterns restricted to nerve distribution and documented nerve fiber dysfunction. Among them four (3.03%) had sensitization of C-nociceptors, seven (5.3%) had central release of nociceptive input, and 35 (26.52%) probable ectopic nerve impulse generation. The atypical group (65.1%) displayed weakness with interrupted effort; non-anatomical hypoesthesia and hyperalgesia; hypoesthesia or paresis reversed by placebo, or atypical abnormal movements, and physiological normality of motor and sensory pathways. *Conclusions* – Spatiotemporal features of neuropathic hyperalgesia constitute key criteria for differential diagnosis between CRPS II and I and, together with other behavioral sensorimotor features, signal psychogenic pseudoneurological dysfunction vs structural neuropathology. 'Neuropathic' hyperalgesias may reflect neuropathological or psychopathological disorders.

R. J. Verdugo[1,2], L. A. Bell[1], M. Campero[1,2], F. Salvat[3], B. Tripplett[1], J. Sonnad[1], J. L. Ochoa[1]

[1]Oregon Nerve Center at Legacy Good Samaritan Medical Center, Departments of Neurology and Neurosurgery, Oregon Health and Science University, Portland, OR, USA; [2]Department of Neurology, Faculty of Medicine, Universidad de Chile, Santiago, Chile; [3]Department of Neurology, Raul Carrea Institute for Neurological Research, FLENI, Buenos Aires, Argentina

Key words: neuropathic pain; complex regional pain syndrome; hyperalgesia; allodynia; somatization

José L. Ochoa, The Oregon Nerve Center, Good Samaritan Medical Center, 1040 NW 22nd Ave., Suite 600, Portland, Oregon 97210, USA
e-mail: jochoa@nervesense.net

Accepted for publication July 22, 2004

There is increasing awareness that the pathophysiological basis for neuropathic pains following peripheral injury is multifactorial (1, 2) and both peripheral and central determinants are recognized. There has been little recognition of the fact that the apparent uniform clinical profile of 'neuropathic' patients is actually bisected into discrete groups after formal neurological evaluation. In one group, anatomical, physiological and pathological analyses of the nervous system predict the clinical features, prognosis, and response to management. The other group departs from the anatomical principles; symptoms often worsen paradoxically with time, rather than improve with natural repair; become refractory to all therapeutic measures; and when tested through objective neurophysiological methods, the motor and sensory pathways function normally even when voluntary movement and reported sensation may appear defective or even abolished clinically. Controversy surrounds the medical nature of the second group, which, in descriptive terminology, is labeled complex regional pain syndrome type I (CRPS I). Given its atypical neurological features, underlying conversion–somatization is intuited (3). Alternatively, based on impressive secondary structural and functional changes documented in the spinal cord or thalamus following experimental primary nerve injury or inflammation, a central neuronal disorder is indicated by many. Critics of the psychoneurological viewpoint fear that the persistent pain might be incorrectly dismissed as being of psychological origin and pointedly remind that inability to discern an 'organic' explanation does not prove psychological causation (4). The counterargument emphasizes the inexistence of anatomophysiological tests to specifically diagnose CRPS I and the absence of a valid animal model for it; what are

available are models of peripheral nerve injury, which CRPS I patients lack. These contrasting theories, however, indicate a central nervous system disorder in common, differing only in its hypothetical location: sensory nuclei vs cerebrum.

Here we focus on hyperalgesia/allodynia, a prevalent psychophysical feature of neuropathic pain patients that has become a favorite subject in somatosensory research. Hyperalgesia is defined as 'an increased response to a stimulus which is normally painful', while allodynia is defined as 'pain due to a stimulus which does not normally provoke pain' (5). The term allodynia is rejected by some investigators (6) while others suggest that the term hyperalgesia should embrace both allodynia and hyperalgesia proper (2). In the present paper, the term hyperalgesia is used to refer to both allodynia and hyperalgesia, as defined by the International Association for the Study of Pain (IASP) (5).

The present neurological and physiological study of a large cohort of patients with chronic neuropathic pain, reveals that in the clinic it is possible to explicitly ascertain equivalents of structural pathology as well as the presence of psychogenic dysfunction behind neuropathic hyperalgesias.

Patients and methods

The present series was extracted from an overall population of 376 consecutive patients referred to the Oregon Nerve Center between January 1998 and December 2000 for evaluation of chronic painful complaints with neuropathic characteristics. All patients underwent a uniform evaluation protocol as described previously (7–9). Inclusion criterion was the presence, on neurological examination or laboratory testing, of cutaneous hyperalgesia to mechanical (dynamic, static or punctate), cold, or heat stimuli. Dynamic mechanical hyperalgesia was defined as an unpleasant, not necessarily painful, sensation evoked by light stroking of the skin. Static mechanical hyperalgesia was defined as a painful sensation in response to sustained gentle pressure on the skin (10). Punctate hyperalgesia was defined as an exaggerated painful sensation elicited by pinprick. Cold hyperalgesia was defined as an exaggerated painful sensation evoked by low-temperature stimulation during quantitative somatosensory thermal test [Marstock method; (11)]. Heat hyperalgesia was defined as an exaggerated painful response evoked by elevation of the stimulus temperature (12).

A total of 132 patients fulfilled the inclusion criteria. There were 81 females and 51 males (mean age 45.7 years, range 18–85). After informed consent, all patients underwent a standard clinical protocol for the evaluation of the function of motor, sensory and autonomic systems. Depending on the emerging profile, the evaluation was followed by conventional nerve conduction tests (130 patients), needle electromyography (105 patients), measurement of somatosensory evoked potentials (57 patients), transcranial magnetic stimulation of motor pathways (81 patients), quantitative somatosensory thermotest (QST) (127 patients), infrared telethermography (103 patients), placebo-controlled somatic nerve blocks (60 patients) and placebo-controlled (inert and active) sympathetic blocks (62 patients). Thus, the vast majority of patients were tested using standard electrophysiological and psychophysical methods for detecting peripheral nerve fiber dysfunction. Additional methods to detect central motor and sensory dysfunction were reserved for patients without peripheral pathology.

The types of cutaneous hyperalgesias were: dynamic mechanical hyperalgesia, 74 patients; static mechanical hyperalgesia, 53; punctate hyperalgesia, 35; cold hyperalgesia, 55; and heat hyperalgesia, 37 patients. Many patients expressed more than one kind of cutaneous hyperalgesia.

Results

Dynamic mechanical hyperalgesia

Dynamic mechanical hyperalgesia ('brush-induced' allodynia) was found in 74 of 132 (56.06%) patients. In 20 of the 74 patients (27.03%), comprehensive clinical and laboratory evaluation documented some peripheral nerve pathology that explained the symptom. This group included six cases with peripheral painful polyneuropathy, in whom dynamic hyperalgesia was present in bilateral stocking distribution. The remainder had single peripheral nerve injury (nine patients), radiculopathy (three patients), mononeuropathy multiplex (one case) and multifocal motor neuropathy (one patient). In all 20 patients, the areas of dynamic mechanical hyperalgesia remained confined to the peripheral nerves affected, without expansion into other territories.

In 46 (62.6%) patients with dynamic mechanical hyperalgesia, clinical and laboratory evaluation not only disclosed a normal function of peripheral and central sensory and motor pathways but also positive signs recognized as non-organic ['psychogenic'; Table 1; (13)], including give-way weakness without significant pain (7, 14, 15), tremor, 'shakiness' and muscle spasms of ostensibly non-organic semeiology (16), extensive non-anatomical areas of

Table 1 Signs of non-organic dysfunction in patients with physiological evidence of normality of peripheral and central sensory and motor pathways

	Dynamic mechanical		Static mechanical		Punctate		Cold		Heat	
Type of hyperalgesia	No nerve injury	Minor nerve injury	No nerve injury	Minor nerve injury	No nerve injury	Minor nerve injury	No nerve injury	Minor nerve injury	No nerve injury	Minor nerve injury
Give-way weakness without pain	29	4	20	4	15	1	21	4	17	2
Abnormal psychogenic movements	11		11		4		8	2	5	1
Non-anatomical cutaneous hypoesthesia	24	4	15	2	11	1	21	1	18	1
Normal two-point discr. threshold with severe hypoesthesia	12		9		4		4		7	1
Reversal of hypoesthesia after placebo	9	3	6	1	5		9		8	1
Reversal of weakness after placebo	9	4	8	2	8		8	2	6	

Table 2 Distribution of types of cutaneous hyperalgesia among patients with and without nerve injury, with and without expansion beyond anatomical nerve territories

	Patients with nerve injury		Patients without nerve injury		Patients with very minor nerve injuries	
Type of hyperalgesia	Expanded	Not expanded	Expanded	Not expanded	Expanded	Not expanded
Dynamic mechanical	0	20	33	13	8	0
Static mechanical	0	15	26	7	5	1
Punctate	0	11	23	0	1	0
Cold	0	14	18	19	4	0
Heat	0	8	15	12	2	0

cutaneous hypoesthesia to pinprick and/or light touch (13, 17, 18), normal two-point discrimination threshold in areas of profound psychophysical hypoesthesia, reversal of severe cutaneous hypoesthesia after inert placebo or active drug administration during local anaesthetic or sympathetic block (9), dramatic improvement of weakness, or motor paralysis after placebo or any irrelevant active drug administration. Three of these patients were known to be substance abusers and another two were found to be malingerers by a secret video surveillance. In 33 (71.74%) patients with positive evidence of non-organic components, the areas of dynamic mechanical hyperalgesia expanded with time to involve extensive territories without recognizable peripheral dermatomal distribution (Table 2). Additionally, eight patients showed striking variation of intensity of the hyperalgesia with distraction, or upon repetition of the neurological examination.

Eight patients had minor peripheral nerve pathology that could not account for the extensive or distant neuropathic display. This group included one patient with a minor C6 radiculopathy, one with a mild ulnar nerve lesion and one with mild entrapment of the median nerve: all three exhibited extensive areas of mechanical hyperalgesia involving the entire upper extremity, including the shoulder. Four patients had a minor nerve lesion in remote body segments. One patient who complained of severe pain in the entire left upper extremity after a minor work injury, had a post-polio syndrome also. Like the group with neurological normality, these patients also exhibited positive signs of non-organic pseudoneuropathic dysfunction (Table 1).

Static mechanical hyperalgesia

Static mechanical hyperalgesia was detected in 54 (40.91%) of the 132 patients. Only 15 (27.78%) patients with static hyperalgesia had evidence of peripheral nerve pathology accounting for the neuropathic syndrome featuring static mechanical hyperalgesia. In this group, there were six patients with painful polyneuropathy, five of whom expressed additional heat hyperalgesia. These are characteristics of the ABC syndrome due to the sensitization of C-nociceptors (19, 20). One patient expressed cold hyperalgesia and sympathetic denervation supersensitivity in the feet, as described in the 'triple cold syndrome' (21). In all these patients with painful polyneuropathy, static mechanical hyperalgesia was detected in bilateral stocking distribution and was not associated with dynamic mechanical hyperalgesia. In nine patients, there was focal pathology including one case of cervical radiculopathy. In all these 15 patients, the area of static mechanical hyperalgesia was restricted to the normal anatomical territory of the affected nerve trunk or root. In three of these cases, static mechanical hyperalgesia was associated with dynamic or punctate hyperalgesia, plus heat hyperalgesia in one and cold hyperalgesia in another.

In 33 (61.11%) patients with static mechanical hyperalgesia, there was evidence of normality of function of peripheral and central sensory and motor pathways and positive evidence of non-organic dysfunction (Table 1). Anecdotally, two patients displayed a nocebo effect, developing atypical muscle spasms during saline administration. Moreover, in 26 (78.79%) patients with positive evidence of psychogenic dysfunction, the areas of static mechanical hyperalgesia expanded with time far beyond the territory of a peripheral nerve trunk or root.

Six patients with static mechanical hyperalgesia harbored a minor nerve injury that could not account for the expansive neuropathic symptom complex. These patients also had a positive evidence of non-organic dysfunction (Table 1). Five of these six patients exhibited extensive non-dermatomal distribution of static hyperalgesia.

Punctate mechanical hyperalgesia

Punctate mechanical hyperalgesia was present in 35 (26.52%) of 132 patients. In 11 (31.43%) patients with punctate hyperalgesia, there was documented peripheral nerve pathology determining the hyperalgesia. In seven of these patients, punctate hyperalgesia was associated with dynamic and/or static mechanical hyperalgesia, in two cases punctate hyperalgesia coexisted with cold hyperalgesia and in one with heat hyperalgesia. Only one patient had a painful polyneuropathy, expressing punctate hyperalgesia in stocking distribution. In nine patients, the cause of the neuropathic painful syndrome was a focal peripheral nerve injury and in one a post-surgical thoracic radiculopathy. In all these 11 cases, punctate hyperalgesia remained confined to the normal anatomical territory of the affected nerves or root.

In 23 (65.71%) patients with punctate hyperalgesia, the symptom occurred in the realm of normal function of peripheral and central afferent and efferent pathways and positive evidence of non-organic (psychogenic) dysfunction (Table 1).

One woman with punctate mechanical hyperalgesia had a minor sensory polyneuropathy detected electrophysiologically. She complained of incapacitating pain in the entire right lower extremity after a minor injury at work. She exhibited give-way weakness and total loss of cold and warm sensation in stocking distribution in the right leg.

Cold hyperalgesia

Cold hyperalgesia was found in 55 (41.67%) of 132 patients. In 14 (25.45%) patients with cold hyperalgesia, there was evidence of peripheral nerve pathology behind the neuropathic syndrome. Nine of them were found to have a polyneuropathy. In these patients, cold hyperalgesia was frequently associated with paradoxical hot burning sensation ['triple cold syndrome'; (21)]. In all nine patients, the cold hyperalgesia was present distally in both lower extremities. In six patients, there was a focal peripheral nerve lesion-caused cold hyperalgesia. One of them also had paradoxical hot burning sensation and impaired vasomotor reflex activity, as described in the triple cold syndrome. Only two among these 14 patients expressed concurrent cold and heat hyperalgesia.

Thirty-seven patients with cold hyperalgesia had normal functioning of afferent and efferent pathways, associated with non-organic phenomena (Table 1). In one of these 37 patients, who had undergone several surgical interventions to treat his painful syndrome, a factitious disorder was suspected. In 26 patients there was coexistent mechanical hyperalgesia, with a non-dermatomal pattern of distribution in 20. In 18 cases, cold hyperalgesia was present in an extensive area that did not follow anatomical peripheral nerve or root territories. This is likely an underestimate considering that many patients underwent QST in restricted body segments. Furthermore, three patients showed gross variability in the severity of cold hyperalgesia and one additional patient reported a threshold for cold pain at a warmer temperature than the threshold for specific cold sensation. Strikingly, 23 (62.16%) patients with cold hyperalgesia with evidence of psychogenic disorder expressed simultaneous cold and heat hyperalgesia, a rare finding in patients with organically based neuropathy.

A minor peripheral disorder, that could not explain the severe chronic neuropathic painful syndrome was found in four patients. They all had evidence of non-organic dysfunction (Table 1).

Heat hyperalgesia

Heat hyperalgesia was present in 37 (28.03%) of 132 patients. In eight (21.62%) patients with heat hyperalgesia, peripheral nerve pathology was documented. Four of these had a painful peripheral polyneuropathy. Sensitization of peripheral nociceptors was likely in three of these polyneuropathic patients as they exhibited bilateral hyperthermia of the feet despite available vasomotor sympathetic reflex activity. Two polyneuropathic patients had associated punctate mechanical hyperalgesia, and one had static mechanical hyperalgesia. The remaining four patients had a defined focal nerve

injury as a cause of the painful neuropathic syndrome. Two of these had combined cold and heat hyperalgesia.

Heat hyperalgesia in a background of normal peripheral and central sensory and motor function, plus positive evidence of psychogenic dysfunction was found in 27 (72.97%) patients with heat hyperalgesia (Table 1). Twenty-one patients had associated mechanical hyperalgesia, which in 13 was of non-anatomical distribution. Like cold hyperalgesia, heat hyperalgesia frequently covered a broad and non-anatomical distribution in 15 patients. The frequent association of cold and heat hyperalgesia in this group of patients was mentioned earlier.

The remaining two patients with heat hyperalgesia had a minor nerve injury distant from the painful area. These two also displayed several signs of psychogenic dysfunction (Table 1).

Summary of findings

Results yielded two discrete semeiologic entities: classic neurological vs. atypical. They are each other's antithesis and fulfill criteria for the descriptive entities CRPS II and I, respectively. The group of classic (CRPS II) patients (34.9%) exhibited a coherent positive and negative sensory and motor pattern, invariably restricted to the anatomical distribution of nerve trunks and spinal roots. In them, known equivalents of peripheral nerve pathology were documented objectively through neurological examination and physiological tests. Among these patients, there were four (3.03%) with evidence of sensitization of C-nociceptors (20), seven (5.3%) had a central release of primary nociceptive input (21), and 35 (26.52%) had signs reflecting ectopic nerve impulse generation. Patients in the atypical (CRPS I) group (65.2%) departed from the laws of anatomy, physiology and pathology of the nervous system. They displayed muscle weakness because of interrupted voluntary effort; extensive and fluctuating cutaneous hypoesthesia and hyperalgesia not conforming to nerve or spinal root territories; hypoesthesia reversed by inert or active placebo intervention; atypical abnormal movements; or recovery of muscle weakness in response to placebo. These patients had physiologically normal motor and sensory pathways both in the peripheral and central nervous systems (Table 2).

Discussion

We describe neurological and multiple neurophysiological characteristics of a vast population of neuropathic patients who altogether reported five descriptive types of cutaneous hyperalgesia/allodynia in response to dynamic mechanical, static mechanical, punctate mechanical, cold and heat stimuli. Two contrasting clinical profiles were discerned. As to the descriptive IASP denominations (5) the classic group of patients qualifies for CRPS type II (causalgia) while the second qualifies for CRPS type I (reflex sympathetic dystrophy). The five types of cutaneous hyperalgesia presented in varied combinations and with the same frequency in both groups of patients, with the exception of the combined pattern of cold and heat hyperalgesia which was more common in the atypical group.

Neuropathological meaning of the present populations

Neurological pain may be the natural expression of various primary structural pathologies of the central nervous system (CNS) affecting the spinothalamic pathway (22, 23). This is not the subject of the present study. When the evaluation of seemingly PNS-based 'neuropathic pain' patients abides to a formal neurological protocol, the detection of cardinal subgroups is inescapable. The two emerging categories carry explicit meaning: (i) peripheral pathology causing commensurate pathophysiology (CRPS II), constrasting with (ii) a pseudoneurological health disorder with absence of analogues of peripheral pathology (CRPS I). When in CRPS I patients, the presumed central pathological basis for puzzling negative motor and sensory phenomena (paralysis and sensory loss), associated to pain and hyperalgesia, was investigated through direct electrophysiological means, the evidence negated it (see also 24).

Classic 'CRPS II'

Several pathophysiological mechanisms were identified among the classic group of patients in this series. Sensitization of peripheral nociceptors as the cause of cutaneous hyperalgesia has been documented in clinical (25, 26) and experimental conditions (see 27). Sensitization is one pathophysiological response of cutaneous nociceptors to noxious stimuli (28). In this series, several patients displayed the characteristic profile of pathological nociceptor sensitization, including spontaneous burning pain and redness of the skin caused by antidromically induced cutaneous vasodilatation (20). Patients with sensitized nociceptors express relief of symptoms with exposure to low temperature and worsening with higher temperatures (29). Experimentally the entire clinical picture is

replicated by cutaneous application of capsaicin in humans (30) and recent studies on the vanilloid receptor, involved in the activation of nociceptors by capsaicin, indicate that its responsiveness to mechanical stimulation is facilitated by increased temperature (see 31). The few patients with documented sensitization of peripheral nociceptors had no evidence of neuronal sensitization within the spinal cord or higher centers. These patients showed a strict correlation between discharge of peripheral C-nociceptors and intensity of pain and experienced no expansion of the areas of hyperalgesia (25). A group of patients with cold hyperalgesia associated with cold hypoesthesia displayed the 'triple cold syndrome' (21). In them, dynamic afferent interactions in the CNS explained cold hyperalgesia and paradoxical hot burning sensation. These phenomena develop experimentally after selective blockade of myelinated fibers, including A-delta afferents specific for cold sensation (32). Ectopic generation of impulses (or ephaptic transmission?) is another mechanism in undetermined patients from this group. It is also likely that further primary abnormal biophysical mechanisms will be identified in the future. Occasionally, ectopic impulse generation leading to multiplication of the afferent barrage may be associated with sensitization of C-nociceptors (26).

Differential significance of the sensory profiles

Although superficially similar, when examined formally the clinical features of patients with chronic neuropathic pain caused by peripheral nerve pathology, compared with those of 'neuropathic' patients with evidence of absence of nerve injury, signal cardinally different pathogeneses. When there is clear peripheral nerve injury, the areas of cutaneous mechanical and thermal hyperalgesia never extend to areas of other nerves or roots (33). In all patients with nerve injury, the pain was restricted to the affected nerves with no tendency to spread beyond the innervation territory (34). This finding also matches optimally Moore and Schady's (35) demonstration that intraneural microstimulation of fascicles of severed nerves in patients always evokes painful and non-painful sensations projected to the normal distribution of the affected nerve, even years after injury, at a time when spinal and supraspinal centers must presumably be fully reorganized through neuronal plasticity. Conversely, large and often bizarre areas of mechanical and thermal hyperalgesia are invariably seen in CRPS I patients with clinically and physiologically intact peripheral and central afferent and efferent systems. Why should expansion of hyperalgesia in 'neuropathic' pain occur only when the hypothetical primary nerve pathology, taken in theory to induce, maintain and expand hyperalgesia through a secondary central mechanism, does not exist? Our findings also challenge the evidential power of the aphorism that touch-induced pain must signal central sensitization in the spinal cord.

Psychogenic 'CRPS I'

The pseudoneuropathic atypical group of patients is explicitly recognizable as psychoneurological in origin (3). This diagnosis is not based purely on the absence of evidence of nerve damage, nor on presence of psychopathology, nor even on the record of normal function of afferent and efferent central and peripheral pathways. The diagnosis largely rests on evidence of pseudoneurological dysfunction of brain origin, including: (a) subjective cutaneous hypoesthesia or hyperalgesia which do not follow nerve trunk or spinal root territories (13, 17) in patients with normal peripheral and central electrophysiological parameters, (b) punctual denial while blindfolded of each tactile stimulus within a reportedly anaesthetic area (9), (c) normal report of two-point touch discrimination within areas of reportedly profound tactile hypoesthesia, (d) hypoesthesia reversed by inert or active placebo intervention (9), (e) muscle weakness with interrupted voluntary upper motor drive, in the absence of significant pain (7, 14, 15), (f) atypical abnormal movements with erratic worsening, and relieved with placebo and distraction (16) and (g) recovery of profound muscle weakness with placebo.

Noordenbos and Wall (36) rejected the psychogenic alternative in patients with chronic neuropathic pain unresponsive to nerve grafting: 'we do not accept this easy way out as an explanation of the pain of our patients particularly the four who were continuing active work and successful private lives… these patients, unlike psychiatric patients, did respond to therapies such as local nerve block, transcutaneous stimulation and sympathetic blocks but for periods too brief for useful therapy.' However, in the early 1980s, Noordenbos and Wall (36) had not come to appreciate today's universally acknowledged placebo bias (37). Moreover, whether 'psychiatric' or not, all sorts of 'neuropathic' pain patients often respond in the short term to the placebo effect of blocks, and neurostimulation (see results, 38). Regrettably, psychogenic dysfunction as a potential primary mechanism of causation and maintenance of chronic neuropathic pain is often denied, by taboo,

even when it is acknowledged that for CRPS I 'the mechanism remains unknown' (39). The fact that, in somatization, the brain generates the clinical appearance of a neurological syndrome is often misleading. Psychopathology has become disguised as neuropathology (40). Malingerers who fake CRPS I may pass undetected, as we spotted only three in this series. Classic neurologists knew about, and accepted, abnormal psychoneurological processes in atypical 'neuropathic patients' (22). As Mitchell (41) points out 'in hysteria, the centers are affected, and in many cases of causalgia, when the constitutional disturbance is at its height, these are so excitable that a touch of the skin anywhere, the sound of a step or the rustle of paper, is felt to be unpleasant, and even at times exquisitely painful' (p. 180).

Regarding other studies on patients of this kind, one drawback of many published 'neuropathic pain' series that form the basis for current theories and inspire animal models of painful nerve injury, is their meager clinical evaluation. Motor and sensory phenomena that are so revealing of the nature of the patients are frequently ignored. Among the 123 patients with 'CRPS' pooled from recognized centers, the only criterion used to distinguish between CRPS I and II was a limited electromyogram (EMG)/nerve conduction study. No information is given on other laboratory tests, let alone neurological examination (42). Indeed, management of chronic 'neuropathic pain patients' is often conducted without prior neurological differential diagnosis (43). The refractoriness of a large fraction of 'neuropathic' pain patients to hypothesis-driven, invasive or addictive therapy, betrays current misinterpretation of their authentic neuropathological and psychopathological origins, while highlighting the iatrogenic impact of the current paradigm.

The neuronal cerebral bases of pseudoneurological profiles

The distribution of classic neuropathic and pseudoneuropathic patients found in this series matches the incidence of organically based neuropathic and psychogenic painful syndromes previously described (8). Livingston (44), working with a similar patient population, from the same country and state as the present series, had reported the abundance of atypical profiles eventually labeled 'pseudoneurologic illness'. Shorter (3) wrote: 'although hysteria has been downplayed in official nosology, it remains a robust category…Historical change gives pseudoneurologic illness its plasticity…in the history of changing symptoms what characterizes the twentieth century is the predominance of sensory symptoms: chronic pain and chronic fatigue in particular.' Jänig (45) states that 'CRPS-I can only be understood as a pain syndrome or disease that is actively generated by the brain'. For this type of brain-generated syndrome, no animal model is available (43). Functional imaging of the brain of patients with diagnosed hysterical (motor and sensory) dysfunction and pain, have revealed intromission of limbic circuit activation during impaired motor or sensory tasks. Studies with positron emission tomography (PET) scan show that in hysterical paralysis the areas of brain activation when attempting to move the paralyzed extremity include the premotor area, as in normal movements, but not the primary motor area. Instead, activation of the orbitofrontal and cingulate cortex is observed (46). In hysterical motor and sensory loss and pain, Vuilleumier et al. (47) describe reduction in regional cerebral blood flow in the contralateral thalamus and basal ganglia, suggesting that 'hysterical conversion deficits may entail a functional disorder in striato-thalamocortical circuits controlling sensory-motor function and voluntary motor behavior.' Studies in patients with chronic atypical neuropathic pain 'with predominant affective component' also show abnormal cortical activation in response to painful stimulation, particularly in the anterior cingulate and prefrontal cortex (48). Iadarola et al. (49) describe diminution of metabolism in the contralateral thalamus of atypical patients with chronic 'neuropathic' pain without nerve injury and Apkarian et al. (50) report prefrontal hyperactivity in similar patients they descriptively label CRPS I and empirically adjudicate as being 'sympathetically maintained'. Mailis-Gagnon et al. (51) report abnormal forebrain and limbic activation in patients with intractable pain and the diagnosis of conversion disorder. Further cerebral studies, coupled with comprehensive neurological and psychiatric evaluation will lead to a better understanding and treatment of patients with somatization disorders (52, 53).

Acknowledgement

This study was supported by NIH grant NS 39761.

References

1. Ochoa JL. Pain mechanisms in neuropathy. Curr Opin Neurol 1994;**7**:407–14.
2. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;**353**:1959–64.
3. Shorter E. The borderland between neurology and history. Conversion reactions. Neurol Clin 1995;**13**:229–39.

4. Rowbotham MC. Complex regional pain syndrome type I (reflex sympathetic dystrophy): more than a myth. Neurology 1998;**51**:4–5.
5. Merskey H, Bogduk N. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Task Force on Taxonomy, International Association for the Study of Pain, 2nd edn. Seattle, WA: IASP Press, 1994.
6. Campbell JN, Raja SN, Meyer RA. Painful sequelae of nerve injury. In: Dubner R, Gebhart GF, Bond MR, eds. Proceedings of the 5th World Congress on Pain. Amsterdam: Elsevier, 1988;135–43.
7. Verdugo RJ, Ochoa JL. Use and misuse of conventional electrodiagnosis, quantitative sensory testing, thermography, and nerve blocks in the evaluation of painful neuropathic syndromes. Muscle Nerve 1993;**16**:1056–62.
8. Ochoa JL, Verdugo RJ, Campero M. Pathophysiological spectrum of organic and psychogenic disorders in neuropathic pain patients fitting the description of causalgia or reflex sympathetic dystrophy. In: Gebhart GH, Hammond DL, Jensen TJ, eds. Proceedings of the 7th World Congress on Pain. Seattle, WA: IASP Press, 1994;483–94.
9. Verdugo RJ, Ochoa JL. Reversal of hypoaesthesia by nerve block, or placebo: a psychologically mediated sign in chronic pseudoneuropathic pain patients. J Neurol Neurosurg Psychiatry 1998;**65**:196–203.
10. Ochoa JL, Yarnitsky D. Mechanical hyperalgesias in neuropathic pain patients: dynamic and static subtypes. Ann Neurol 1993;**33**:465–72.
11. Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;**39**:1071–5.
12. Verdugo RJ, Ochoa JL. Quantitative somatosensory thermotest. A key method for functional evaluation of small caliber afferent channels. Brain 1992;**115**:893–913.
13. Walters A. Psychogenic regional pain alias hysterical pain. Brain 1961;**84**:1–18.
14. Lambert EH. Electromyography and electrical stimulation of peripheral nerves and muscles. In: Mayo Clinic Staff, eds. Clinical examination in neurology. Philadelphia, PA: WB Saunders, 1956.
15. Wilbourn AJ. The electrodiagnostic examination with hysteria-conversion reaction and malingering. In: Weintraub MI, ed. Malingering and conversion reactions. Neurologic Clinics of North America, vol. 13. Philadelphia, PA: WB Saunders, 1995;385–404.
16. Verdugo RJ, Ochoa JL. Abnormal movements in complex regional pain syndrome: assessment of their nature. Muscle Nerve 2000;**23**:198–205.
17. Haymaker W, Woodhall B. Peripheral nerve injuries. Principles of diagnosis. Philadelphia, PA: WB Saunders, 1953.
18. Fishbain DA, Goldberg M, Steele R, Rosomo H. Chronic pain patients and the nonorganic physical sign of nondermatomal sensory abnormalities (NDSA). Psychosomatics 1991;**32**:294–393.
19. Lewis T. Pain. London: The Macmillan Press Ltd., 1942, Facsimile edition 1981.
20. Ochoa JL. The newly recognized painful ABC syndrome: thermographic aspects. Thermology 1986;**2**:65–107.
21. Ochoa JL, Yarnitsky D. The triple cold syndrome. Cold hyperalgesia, cold hypoaesthesia and cold skin in peripheral nerve disease. Brain 1994;**117**:185–97.
22. Dejerine PJ. Sémiologie du système nerveux. In: Traité de pathologie générale. Paris: Masson, 1901;359–1168.
23. Boivie J, Leijon G, Johansson I. Central post-stoke pain-a study of the mechanisms through analyses of the sensory abnormalities. Pain 1989;**33**:87–107.
24. Lacerenza M, Triplett B, Ochoa JL. Centralization in reflex sympathetic dystrophy/causalgia patients is not supported by clinical neurophysiological tests. Neurology 1996;**46**(Suppl.):A169.
25. Cline MA, Ochoa JL, Torebjörk HE. Chronic hyperalgesia and skin warming caused by sensitized nociceptors. Brain 1989;**112**:621–47.
26. Ochoa JL, Serra J, Campero M. Pathophysiology of human nociceptor function. In: Belmonte C, Cervero F, eds. Neurobiology of nociceptors. Oxford: Oxford University Press, 1996;489–516.
27. Perl ER. Alterations in the responsiveness of cutaneous nociceptors. Sensitization by noxious stimuli and the induction of adrenergic responsiveness by nerve injury. In: Willis WD Jr, ed. Hyperalgesia and allodynia. The Bristol-Myers Squibb Symposium on Pain Research. New York: Raven Press Ltd., 1992;59–79.
28. Bessou P, Perl ER. Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. J Neurophysiol 1969;**32**:1025–43.
29. Ochoa JL. Thermal hyperalgesia as a clinical symptom. In: Willis WD Jr, ed. Hyperalgesia and allodynia. The Bristol-Myers Squibb Symposium on Pain Research. New York: Raven Press Ltd., 1992;151–65.
30. Culp WJ, Ochoa JL, Cline M, Dotson R. Heat and mechanical hyperalgesia induced by capsaicin: cross modality threshold modulation in human C nociceptors. Brain 1989;**112**:1317–31.
31. Caterina MJ, Julius D. The vanilloid receptor: a molecular gateway to the pain pathway. Annu Rev Neurosci 2001;**24**:487–517.
32. Wahrén LK, Torebjörk HE, Jørum E. Central suppression of cold-induced C fibre pain by myelinated fibre input. Pain 1989;**38**:313–9.
33. Campero M, Ochoa JL, Pubols L. Receptive fields of hyperalgesia confine to districts of injured nerves: fields 'expand' in 'RSD' without nerve injury (abstract). Soc Neurosc 1992;**18**:287.
34. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. Brain 2001;**124**:587–99.
35. Moore CEG, Schady W. Investigation of the functional correlates of reorganization within the human somatosensory cortex. Brain 2000;**123**:1883–95.
36. Noordenbos W, Wall PD. Implications of the failure of nerve resection and graft to cure chronic pain produced by nerve lesions. J Neurol Neurosurg Psychiatry 1981;**44**:1068–73.
37. Wall PD. The placebo effect: an unpopular topic. Pain 1992;**51**:1–3.
38. Verdugo RJ, Ochoa JL. Placebo response in chronic, causalgiform, neuropathic pain patients: study and review. Pain Rev 1994;**1**:33–46.
39. Stanton-Hicks M. Complex regional pain syndrome (type I, RSD; type II, causalgia): controversies. Clin J Pain 2000;**16**:S33–S40.
40. Ochoa JL, Verdugo RJ. Mechanisms of neuropathic pain: nerve, brain, and psyche: perhaps the dorsal horn but not the sympathetic system. Clin Auton Res 2001;**11**:335–9.
41. Mitchell SW. Injuries of the nerves and their consequences (1872), American Academy of Neurology Reprint Series. New York: Dover Publications, 1965.

42. Harden RN, Bruehl S, Galer BS et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain 1999;**83**:211–9.
43. Ochoa JL. Essence, investigation, and management of 'neuropathic' pains: hopes from acknowledgment of chaos. Replies to Drs. Day, Teasell, Shapiro, and Merskey. Muscle Nerve 1995;**18**:458–62.
44. Livingston WK. Pain Mechanisms. A physiologic interpretation of causalgia and its related states. New York: The Macmillan Company, 1947.
45. Jänig W. CRPS-I and CRPS-II: a strategic view. In: Norman Harden R, Baron R, Jänig W, Bruehl S, Galer BS, Stanton-Hicks M, eds. Complex regional pain syndrome, Progress in pain research and management, vol. 22. Seattle: IASP Press, 2001;3–15.
46. Marshall JC, Halligan PW, Fink GR, Wade DT, Frackowiak RSJ. The functional anatomy of a hysterical paralysis. Cognition 1997;**64**:B1–B8.
47. Vuilleumier P, Chicherio C, Assal F, Schwartz S, Slosman D, Landis T. Functional neuroanatomical correlates of hysterical sensorimotor loss. Brain 2001;**124**:1077–90.
48. Derbyshire SWG, Jones AKP, Devani P et al. Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. J Neurol Neurosurg Psychiatry 1994;**57**:1166–72.
49. Iadarola MJ, Max MB, Berman KF et al. Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. Pain 1995;**63**:55–64.
50. Apkarian AV, Thomas PS, Krauss BR, Szeverenyi NM. Prefrontal cortical hyperactivity in patients with sympathetically mediated chronic pain. Neurosci Lett 2001; **311**:193–7.
51. Mailis-Gagnon A, Giannoylis I, Downar J et al. Altered central somatosensory processing in chronic pain patients with 'hysterical' anesthesia. Neurology 2003;**60**:1501–7.
52. Ron MA. Somatisation in neurological practice. J Neurol Neurosurg Psychiatry 1994;**57**:1161–4.
53. Ron MA. Explaining the unexplained: understanding hysteria. Brain 2001;**124**:1065–6.