Reversal of hypoaesthesia by nerve block, or placebo: a psychologically mediated sign in chronic pseudoneuropathic pain patients

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Abstract

***Objectives*—To gain understanding of the mechanism and meaning of improvement of hypoaesthesia after a diagnostic intervention, and of the nature of the population that displays such a sign.**

***Methods*—Patients with chronic "neuropathic" pain underwent rigorous clinical and laboratory investigations, including placebo controlled local anaesthetic block. Patients displaying profound regional cutaneous hypoaesthesia and pain entered the study through either of two criteria: (*a*) reversal of hypoaesthesia after diagnostic block, (*b*) nerve injury as the cause of hypoaesthesia and pain. The semeiology displayed by these patients together with the behaviour of their sensory phenomena in response to blocks were compared. Three groups were expected: (1) patients with "neuropathic" pain with profound hypoaesthesia reversed by block, but without neuropathy; (2) patients whose hypoaesthesia did not reverse and who had neuropathy as the cause of their sensory dysfunction; and (3) patients whose hypoaesthesia reversed, and had neuropathy.**

***Results*—Two groups emerged: (1) patients with profound hypoaesthesia reversed by block, but without neuropathy (27 patients), and (2) patients whose hypoaesthesia did not reverse and who had a neuropathy (13 patients). No patient with neuropathy was found whose cutaneous hypoaesthesia improved with block. The first group displayed the sensory-motor characteristics of psychogenic pseudoneuropathy. The semeiology of the second group was in keeping with organic neuropathy and displayed no pseudoneurological features. Spontaneous pain was relieved by placebo in 66.6% of the patients in group1 and 53.8% in group 2.**

***Conclusions*—Such reversal of hypoaesthesia is due to a placebo effect, acting on a psychogenic symptom because: (*a*) 27 of 27 patients in which the sign occurred had absence of nerve disease behind the "neuropathic" symptoms, (*b*) In 26 of 27 patients the area of hypoaesthesia was non-anatomical, (c) 16 of 27 patients had other sensory-motor signs that could not be explained as a result of organic pathology (give way weakness and punctual denial of hypoaesthesia), and (d) the phenomenon was not found in patients with organic neuropathy.**

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A chronic painful syndrome is termed "neuropathic" when it associates with various combinations of neurological negative or positive sensory, motor, and vasomotor phenomena. Either organically based disease of peripheral nerves or psychogenic pseudoneurological illness, in addition to fraudulent malingering, may cause the complaint of pains associated with neurological symptoms.[1–4] Placebo controlled diagnostic anaesthetic blocks of various kinds are useful in the clinical investigation of mechanisms of chronic pains with neuropathic characteristics.[5] When combined with thermography the yield of diagnostic anaesthetic nerve blocks is enriched by specification of the particular somatic and vasoconstrictor innervation territory for the targeted nerve.[5–8 10] Whereas symptomatic abolition of psychophysical hyperalgesia is a logical and invariable outcome in areas rendered anaesthetic by effective somatic nerve block, the variable behaviour of subjective spontaneous pain is traditionally taken to differentiate abnormal peripheral versus central underlying mechanisms.[9 10] Intriguingly, in dealing with patients with chronic pain associated with assorted positive and negative sensory, motor, and vasomotor manifestations (CPSMV[11]) the physician occasionally comes across a phenomenon whereby profound cutaneous hypoaesthesia, detected during standard psychophysical examination, may dramatically improve or disappear in response to a diagnostic medical intervention—for example, a placebo controlled local anaesthetic block. Such a phenomenon has certainly been reported in the past[12–19] but the theories proposed only cover part of a range of alternatives, and remain hypothetical. A common denominator for those hypotheses is the assumption that there exists structural pathology of the peripheral nervous system causing the displayed sensory-motor dysfunction and the pain. The reversible hypoaesthesia would be hypothetically determined by a secondary dynamic functional block in central nervous connections, or even in the nerves themselves.[12 15]

Unpersuaded by prevailing theories to explain the phenomenon[12–19] we launched the

Table 1 Summary of clinical and laboratory profiles (group I)

Patient/ sex/age	*Site/cause of pain*	*Area of hypoaesthesia*	*Motor examination*	*Nerve conduction*
1/F/54	L foot. Minor injury at work	L leg. Stocking distribution	L foot: give way weakness	S:bilat sural and superficial peroneal Ns normal M: bilat peroneal and post. tibial Ns normal
2/M/35	L arm. Minor injury at work	Irregular glove up to L shoulder	L upper limb: give way weakness	S/M: bilat median, ulnar and radial Ns normal
3/F/35	R arm and neck. Minor injury at work	Irregular glove up to neck, sparing thenar eminence	R upper limb: give way weakness	S/M: bilat median and ulnar Ns normal
4/M/21	R hand dorsum. Minor injury at work	Medial palm and dorsum of R hand	Mild weakness of right hand with pain	S/M: bilat median, ulnar and radial Ns normal
5/F/27	R forearm. Minor injury at work	Irregular glove in R hand	R upper limb: give way weakness	S/M: bilat median and ulnar Ns normal
6/F/28	R arm. Physical exercise	Medial R upper extremity, L forearm, R foot	Normal	S/M: bilat ulnar Ns normal
7/F/29	L calf and foot. Minor injury at work	Lateral L foot and posterior leg	Mild wasting of L EDB and gastroc muscles. Mild weakness of L foot dorsiflexion	S: absent L sural, ↓ ampl. L sup. peroneal N. M: bilat peroneal Ns normal
8/F/27	L ankle. Twisting at work	Lateral L foot	Normal	S: Absent L sural N response
9/M/53	R arm. Minor injury at work	Irregular glove up to R wrist	Not testable in R upper limb because of pain	S/M: mildly prolonged distal latency L median N. Normal bilat ulnar Ns.
10/F/31	Both hands. Strenuous manual work	Irregular bilateral glove up to wrists	Normal	S/M: bilat median Ns normal
11/F/28	Both arms. Manual work	Irregular glove up to R forearm	Both upper limbs: global give way weakness	S/M: bilat median and ulnar Ns normal
12/F/30	Both hands, R shoulder, L elbow. Manual work	L shoulder, posterior aspect	Normal	S/M: bilat median and ulnar Ns normal
13/F/42	R hand. Manual work	R face, hemithorax, shoulder, medial arm and forearm	R forearm and hand: give way weakness	S/M: bilat median and ulnar Ns normal
14/F/35	L arm. No precipitating event	Irregular glove up to L elbow	Normal	S/M: residual L carpal tunnel. Normal ulnar Ns
15/F/43	R arm. Minor injury at work	Irregular glove up to R posterior forearm	R upper limb: global give way weakness	S/M: bilat median, ulnar and radial Ns normal
16/F/37	L cheek after eye infection	L cheek, ear and lower jaw sparing lip	Normal	Symmetric blink reflexes
17/F/36	R arm. Fall at work	Irregular area in R shoulder.	R upper limb: global give way weakness	S/M: bilat median and ulnar Ns normal
18/F/50	Low back. Minor injury at work	R lumbar area and lateral thigh, leg and foot	R lower limb: global give way weakness	S: bilat sural Ns normal. M: bilat peroneal Ns normal. Normal H refl.
19/F/32	R foot. Sold fracture lateral malleolus at work	Lateral R foot and leg	Normal	S: bilat sural N normal. M: bilat peroneal Ns normal
20/F/37	Both arms. Strain at work	Dorsum of both hands: part of radial and ulnar nerve territories	Normal	S/M: bilat median and ulnar Ns normal
21/F/58	R wrist and thumb. Strain at work	Irregular glove up to R wrist	R upper limb: global give way weakness	S/M: bilat median and ulnar Ns normal
22/F/39	L arm. Fall at work	L shoulder, neck and upper limb sparing ring finger	Not testable in L upper limb because of pain	S/M: bilat median and ulnar Ns normal
23/F/48	Low back. No precipitating event	Lateral thighs and buttocks bilateral, R lateral abdomen	Both lower limbs: global give way weakness	S: bilat femoro cutaneous, sural, ulnar Ns normal. M: ↓amp.CMAP, no F response in L peroneal N
24/F/53	L hand. Repetitive motion at work	Irregular area, dorsal and palmar L hand	L upper limb: global give way weakness	S/M: bilat median Ns normal
25/F/45	R arm. Mild stretch at work	L shoulder and medial half of L middle, ring , and little fingers	Normal	S/M: bilat median and ulnar, axillary Ns normal
26/M/34	R arm. Lifting at work	Radial dorsum of the R hand	Normal	S/M: bilat median and radial Ns normal
27/F/34	L arm. Minor injury at work	L hemibody. also deafness on the left	L hemibody: global give way weakness including rotation of head to L	S: bilat sural and median Ns normal. M: bilat peroneal and median Ns normal

R=right; L=left; S=sensory; M=motor; N=nerve; bilat = bilateral; Ns = nerves.

present study through assessing placebo-controlled diagnostic somatic nerve blocks in patients with chronic "neuropathic" painful syndromes. Patients fulfilled currently accepted criteria either for reflex sympathetic dystrophy (complex regional pain syndrome-CRPS-type I)[20] or for causalgia (complex regional pain syndrome type II).[20]

Methods

The present patient population was extracted from an overall population of 407 patients referred to the Neuromuscular Unit, Good Samaritan Hospital between January 1991 and December 1992 for evaluation of a chronic painful syndrome with seemingly neuropathic characteristics. All patients underwent a uniform protocol, including detailed neurological examination followed by conventional electrophysiological tests for function of large calibre sensory and motor fibres,[21] quantitative somatosensory thermotest for function of small calibre afferent channels,[22 23] and infrared telethermography and laser Doppler capillary flowmetry for assessment of neural vasomotor function.[3 24 25]

Single blind placebo controlled somatic local nerve block was administered to over 100 patients at the end of the clinical and laboratory investigation. The procedure can be summarised as follows: at baseline, subjective magnitudes of spontaneous subjective pain and dynamic and static psychophysical mechanical hyperalgesias[26] were estimated by the patient in a 0–10 verbal pain scale. Patients were also asked to estimate degree of pinprick and/or light touch hypoaesthesia as a percentage of normal sensation tested in a homologous con-

Table 1 continued)

EMG	*QST*
L lower limb: normal	Bilateral feet: normal
L upper limb: interrupted effort (even without pain)	L hand: inconsistent mild warm hypoaesthesia
R upper limb: interrupted effort (even without pain)	Bilateral hands: normal
Not performed	R thenar and radial dorsum of the hand: mild cold and warm hypoaesthesia
L upper limb: interrupted effort (even without pain)	Bilateral forearms: normal
Not performed	bilateral arms and hands: normal
L lower limb: normal	Bilateral legs: normal
Not performed	L foot: warm and cold hypoaesthesia
Not performed	Bilateral hands and feet: normal
R hand: normal	R thenar: mild cold and warm hypoaesthesia
R upper limb: interrupted effort (even without pain)	R shoulder: mild warm hypoaesthesia
Not performed	Bilateral hands and shoulders: normal
Not performed	Bilateral hands: normal
Residual dennervation L APB	Bilateral hands: normal
R upper limb: interrupted effort (even without pain)	Bilateral hands: normal
Not performed	Bilateral cheeks: normal
R upper limb: interrupted effort (even without pain)	Bilateral hands and shoulders: normal
L lower limb: interrupted effort (even without pain)	R lateral thigh: mild cold and warm hypoaesthesia
Not performed	R lateral foot: erratic warm hypoaesthesia
Not performed	Bilateral hands: normal
R hand: interrupted effort (even without pain)	Bilateral hands: erratic cold and heat hyperalgesia
Not allowed by patient	Bilateral thenar eminences: mild cold and warm hypoaesthesia
Spontaneous activity (fibrillation in L EDB)	Bilateral hands and feet: normal
L upper limb: interrupted effort (even without pain)	Bilateral hands: normal
Not performed	Bilateral shoulders and hands: normal
R forearm: interrupted effort (even without pain)	Bliateral hands: normal
L upper limb interrupted effort (even without pain)	Bilateral hands and feet: normal

tralateral site. They were informed that an injection would be given close to a nerve serving the area of maximal sensory dysfunction as a means of investigating the source of complaints. Then, 2–3 ml of saline were injected subcutaneously, for an inert placebo control, close to a nerve serving the area of maximal symptoms. After an interval of 30 minutes, the magnitude of spontaneous and stimulus evoked pains, as well as cutaneous hypoaesthesia, were re-evaluated separately. Next, 2% lidocaine was injected close to the site of saline injection, aimed at a nerve serving the symptomatic area. After a second interval of 30 minutes the indices were re-evaluated.

Forty patients entered the present study as they volunteered regional light touch or pinprick hypoaesthesia with 50% or less residual sensation and in addition met one or both of the following criteria: (a) they harboured evidence of organic nerve disease as the cause of their hypoaesthesia and pain; (b) their cutaneous hypoaesthesia improved significantly after placebo or lidocaine injection.

Although many patients expressed cutaneous hyperalgesia this was not considered an entry criterion because the aim of the study was to evaluate the behaviour of the cutaneous hypoaesthesia. As patients without organically based neuropathy whose hypoaesthesia was not reversed by nerve block or placebo did not meet the entry criteria, only three groups were anticipated to emerge: (1) patients displaying profound hypoaesthesia reversed by placebo or lidocaine, who did not have organic neuropathy; (2) patients whose hypoaesthesia was not reversed and who had a structural neuropathy behind their sensory dysfunction; and (3) patients whose cutaneous hypoaesthesia was reversed by placebo or lidocaine injection and had an established neuropathy.

Results

No patients were found that met both entry criteria—that is, presence of nerve injury and reversal of hypoaesthesia in response to nerve block or placebo. Therefore only two groups became available for analysis and comparison. Group 1 patients expressed improved hypoaesthesia in response to block and had no nerve injury as the cause of the sensory dysfunction (27 cases). In group 2 patients the hypoaesthesia did not improve and all harboured a neuropathy as its determinant (13 cases).

GROUP 1

This population included 23 women and four men (age 21–58 years; mean 37.8, table 1) presenting an apparently neuropathic regional chronic painful syndrome descriptively diagnosable as reflex sympathetic dystrophy (RSD) or CRPS I: 19 in the upper limbs (11 right, four left, and four both); six in the lower limbs (one right and three left); one in the left cheek and two in lumbosciatic distribution (table 2). Comprehensive clinical and laboratory evaluation documented normality of function of large and small calibre sensory, motor, and autonomic fibre systems in 24 of 27 patients; in patients 7, 14, and 23 incidental nerve injuries were found; but these could not explain the syndrome in patients 14 and 23. The exception, patient 7, had definite signs of sural nerve injury affecting large calibre afferent fibres (non-recordable sensory nerve action potential) and surgical exploration disclosed a traumatic sural neuroma confirmed histologically. In patient 14 there was electrophysiological evidence of carpal tunnel syndrome due to an intraneural fibroma confirmed through surgical exploration and nerve biopsy. After surgery this patient developed extensive hypoaesthesia beyond median nerve distribution. In patient 23 there were electrophysiological changes in keeping with a minor S1 radiculopathy that did not account for the patient's painful syndrome (table 1).

Needle EMG of clinically weak muscles showed the absence of neurogenic signs in 14

Table 2 Outcomes of sensory dysfunction (group 1)

Patient	Nerve injury	Dermatomal Hypoaesthesia	Hypoaesthesia	Nerve blocked and site	Normal sensation (%)			Spontaneous pain		
					Baseline	Post placebo	Post lidocaine	Baseline	Post placebo	Post lidocaine
1	No	No	L P	L Post. tibial, ankle	45	100	100	8	0	0
2	No	No	L P	L median, elbow	50	100	100	4	0	0
3	No	No	L P	R median, elbow	50	50	100	4	4	2
4	No	No	L P	R radial, elbow	50	100	100	4	2	0
5	No	No	P	R ulnar, wrist	50	50	100	6	3	2.5
6	No	No	L P	R ulnar, wrist	50	90	100	5	0	0
7	Yes	No	L P	L sural , leg	25	100	100	7.5	2.5	0
8	No	No	L P	R radial, wrist	20	100	100	10	5	0
9	No	No	P	R ulnar, elbow	50	50	100	7.5	5.5	0
10	No	No	L P	R median, wrist	20	100	100	2	0	0
11	No	No	L P	Cervical area, back	50	100	100	8.5	3	3
12	No	No	p	R median, elbow	50	100	100	4	1.5	1.5
13	No	No	L P	R median, wrist	50	100	100	6	0	0
14	Yes	No	L P	R median, wrist	5	5	100	5	10	10
15	No	No	P	R ulnar, wrist	25	50	100	5	1	0
16	No	No	L P	L infraorbital, cheek	50	70	100	—	—	—
17	No	No	L P	Cervical area, back	10	10	100	7	6	0.5
18	No	No	L P	Lumbar area	45	45	100	10	5.5	5
19	No	No	L	R sural, leg	30	100	100	6.5	2	2
20	No	No	P	R radial, elbow	40	80	80	4.5	2	0
21	No	No	L	L median, elbow	50	100	100	8.5	4	0
22	No	No	L P	L radial, elbow	5	5	100	10	8	7
23	Yes	No	L P	Low back	50	100	100	10	0	0
24	No	No	L	L median, wrist	50	100	100	5	2	0
25	No	No	P	R shoulder	5	75	75	7	2	1.5
26	No	Yes	P	R radial, elbow	15	15	100	2.5	2.5	1.5
27	No	No	L P	L median, elbow	20	20	100	5	5	0

L=light touch, P=pinprick.

of the 16 patients tested (table 1). In 11 of them, there was normal motor unit recruitment punctuated by cyclical interruptions of voluntary drive in the absence of pain, indicating impaired cortical volitional effort.[5 27 28] In patient 14 there were giant polyphasic motor unit potentials in the left abductor pollicis brevis muscle without signs of active denervation. In patient 23 there were fibrillations restricted to the left extensor digitorum brevis muscle, together with diminution of amplitude of CMAP and absence of F wave response in the left peroneal nerve, in keeping with a mild S1 radiculopathy that could not account for the extensive area of psychophysical cutaneous hypoaesthesia volunteered in the abdomen, buttocks, and thighs. Thermography and laser Doppler testing of vasomotor reflexes were normal in all patients in group 1.

Twenty six of the 27 patients complained of spontaneous baseline pain, rated between 2 and 10/10 (average 6.3). By selection criteria all 27 patients volunteered cutaneous hypoaesthesia to light touch and/or pinprick within the symptomatic segment, estimated as between 5% and 50% of normal sensation (average 36.2% residual). Three patients expressed hypoaesthesia only to light touch, seven only to pinprick, and 16 to both submodalities (table 2). In 26 of the 27 patients the area of hypoaesthesia did not follow a recognised cutaneous nerve or root territory. In one patient (26) the area of pinprick hypoaesthesia matched the documented distribution of the patient's superficial radial nerve. However, he expressed complete normalisation of profound pinprick hypoaesthesia after a first administration of lidocaine, despite failure to block the nerve, implying that the response was an active placebo effect.[29] Three patients punctually signalled with a "no" every light tactile stimulus applied within the profoundly hypoaesthetic area, while blindfolded.

Injection of saline improved significantly the volunteered cutaneous hypoaesthesia, by more than 50%, in 18 of the 27 patients. Thirteen of them volunteered complete recovery of hypoaesthesia. After lidocaine all 27 patients volunteered significant improvement of cutaneous hypoaesthesia beyond the area of induced anaesthesia.. Twenty five of them expressed complete recovery of sensation (the figure illustrates a striking example) whereas two volunteered mild residual hypoaesthesia (table 2). Notably, improvement of sensation was not necessarily associated with diminution of pain (exceptions: patients 14 and 26, table 2).

Placebo injection also resulted in significant overall relief of spontaneous pain from an average of 6.3 (SD 2.32) at baseline to 2.86 (SD 2.58) for the 27 patients ($p<0.001$, paired t test). Lidocaine administration further diminished overall spontaneous pain to 1.36 (SD 2.53); $p<0.001$). Eighteen patients volunteered significant relief of spontaneous pain in response to saline (66.6%) and five in response to lidocaine. Three patients expressed no significant pain relief. One patient without spontaneous pain volunteered complete relief of mechanical hyperalgesia in response to saline.

ILLUSTRATIVE CASE

Patient 6, (figure)

A 27 year old woman developed pain and numbness in the right upper extremity after unusual physical exercise. She had been given the diagnosis of reflex sympathetic dystrophy. Neurological examination disclosed scattered areas of pinprick and light touch hypoaesthesia in both upper extremities, neck, and right foot (50% of normal sensation). Laboratory investigation yielded normal results for function of peripheral large and small calibre myelinated

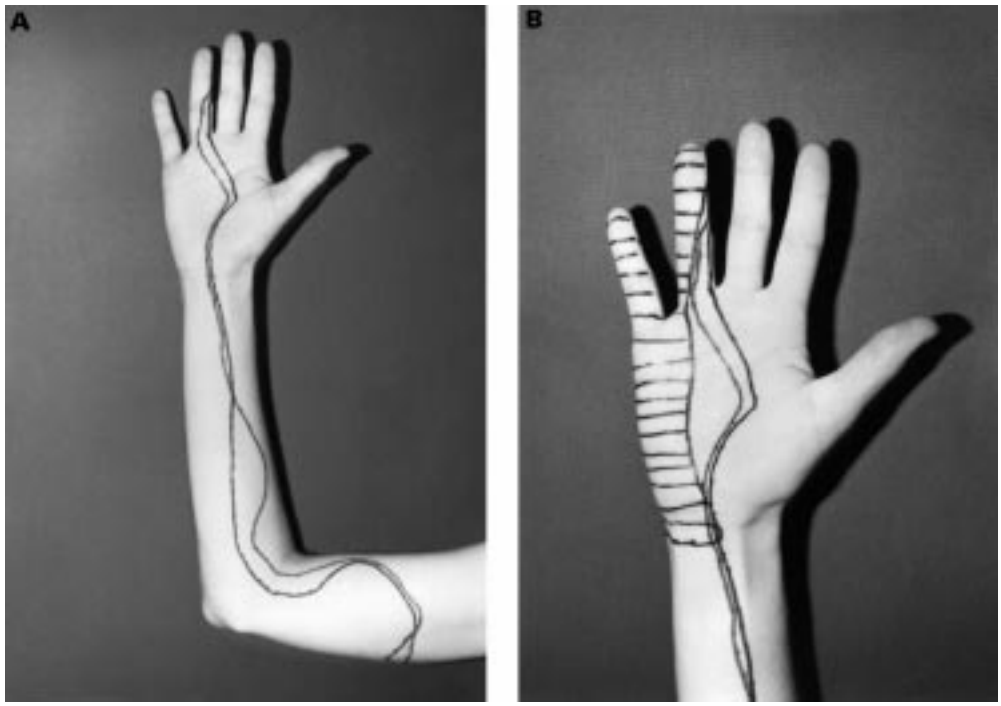

Figure 1 Patient 6 (A) Area of light touch and pinprick hypoaesthesia (50% of normal sensation) at baseline. (B) After lidocaine block of the ulnar nerve at the wrist, the resulting cutaneous hypoaesthesia was restricted to normal ulnar nerve cutaneous distribution. The pre-existing hypoaesthesia disappeared.

and unmyelinated motor, sensory, and sympathetic fibres. At baseline, spontaneous pain was rated as 5 in the 0–10 pain scale. After injection of 3 ml saline in the ulnar side of the anterior right wrist, spontaneous pain and extensive cutaneous hypoaesthesia, between hand and upper arm, disappeared completely. An area of pinprick and light touch anaesthesia, with typical ulnar nerve distribution, developed after lidocaine block of that nerve at wrist level. Pinprick and light touch sensation remained normal beyond the area.

GROUP 2

The group of patients with peripheral nerve injuries causing pain and cutaneous pinprick or light touch hypoaesthesia that did not improve in response to placebo controlled nerve block, included six women and seven men (aged 39–77 years; mean 53.0). Their neuropathic painful syndrome affected an upper extremity in five (one right, three left); the lower extremities in seven (two right, four left, one both); and the thoracic region in one. Among the population of patients with painful nerve injury, it was rare to find instances of injury to a single nerve associated with cutaneous hypoaesthesia deeper than 50% of normal sensation. However, most patients included in this study had hypoaesthesia rated close to 50% of normal cutaneous sensation. Patients 10 and 11, who had total tactile and pinprick anaesthesia, had damage to more than one neighbouring nerve. All patients with nerve injury displayed areas of hypoaesthesia in keeping with the normal anatomical territory. None volunteered improvement of hypoaesthesia in response to placebo or lidocaine, including seven patients (53.8%) who expressed significant improvement of pain in response to inert placebo administration. After local anaesthetic nerve block, the resulting area of cutaneous hypoaesthesia always matched the previous area of hypoaesthesia, exceptions being patients 6 and 11 in whom no satisfactory nerve block was achieved. In patient 6 an attempt to block the lateral femoral cutaneous nerve resulted in blockade of the femoral nerve, with development of hypoaesthesia in the anterior thigh adjacent to the area of pre-existing cutaneous hypoaesthesia. Nevertheless the patient did not volunteer significant improvement of such hypoaesthesia.

Discussion

Patients with nerve injury displayed a textbook clinical and laboratory pattern of sensory, motor, vasomotor, and spinal reflex dysfunction. After all, standard knowledge on nerve anatomy, physiology and pathology has to a large extent been derived from studies of human nerve injuries.[30–33] Whereas in patients with nerve injury the pain might be relieved through a placebo effect, it would have been intriguing if their structurally based sensory and motor deficits had reversed through activation of whatever system in the brain subserves the transient placebo response. Patients who displayed an atypical sensory, motor, vasomotor, and reflex clinical profile did not harbour nerve pathology, an event which, given the magnitude of the clinical profile, could not have evaded standard neurophysiological laboratory tests. The phenomenon of improvement of hypoaesthesia by placebo or lidocaine injection only occurred in these "neuropathic" patients without nerve injury (group 1).

Transient reversal of cutaneous hypoaesthesia after a medical intervention has been described in the past. In 1960 Nathan[12]

reported improved light touch and pinprick hypoaesthesia, concomitant with relief of pain, after injection of a few ml of local anaesthetic in five patients with "neuropathic" painful syndromes of diverse aetiology. He assumed that they harboured organic nerve injury. Nathan proposed that this phenomenon was a physiological consequence of pain relief. In reporting sensory function in 10 patients with chronic neuropathic pain, Lindblom and Verrillo[15] stated that a patient without evidence of peripheral nerve lesion experienced normalisation of thresholds for cold and warm sensations during pain relief induced by vibration. The authors concluded that the hypoaesthesia was due to a central functional block associated with the pain. Later, Lindblom[17] reported improvement of thermal hypoaesthesia and heat hypoalgesia in the hand of a patient during regional guanethidine sympathetic block. The author concluded that the improved hypoaesthesia represented a reversible blocking effect on sensory transmission restorable after pain relief.

At variance with the interpretation attributing reversal of hypoaesthesia to pain relief is the finding by Hodge and King[16] in three patients with regional cutaneous hypoaesthesia and anaesthesia after surgery for treatment of local intractable pain. In all three patients the areas of cutaneous sensory deficit diminished in size after oral administration of levodopa even though spontaneous pain actually increased in magnitude. More recently Marchettini *et al*[18] reported reduction in the area of cutaneous hypoaesthesia in response to intravenous administration of lidocaine in nine of 10 patients expressing painful syndromes possibly caused by nerve injury. In one there was no shrinkage of cutaneous hypoaesthesia despite relief of pain. The authors attributed improvement of hypoaesthesia to systemic action of lidocaine within the CNS. Moriwaki *et al*[19] recently reported improvement of cutaneous hypoaesthesia and mechanical hyperalgesia in 42 patients with chronic pain of diverse aetiologies. The phenomenon was attributed to relief of pain through different procedures. The authors explained the phenomenon as due to changes in the excitatory and inhibitory zones of receptive fields of wide dynamic range neurons in the dorsal horn. Such an idea would imply that wide dynamic range neurons participate not only in the sensation of pain but also in tactile sensation. Wheras the first concept remains unproved,[34] the second is not thought likely.

Despite contradictions, past hypotheses concur in that improvement of the hypoaesthesia is in some way the consequence of pain relief. Neither the findings of Hodge and King[16] nor our results support this idea. Indeed, improvement of hypoaesthesia occurred in two patients without nerve injury whose pain was not relieved. Of course, the phenomenon did not occur in patients with nerve injury, even in those in whom placebo or lidocaine relieved pain. For the basic findings leading to past hypotheses placebo control was never implemented and the possibility of an active placebo effect was never considered, except by Marchettini *et al.*[18] It is not generally appreciated that patients with chronic neuropathic painful syndromes tend to express a high incidence of inert and active placebo response.[35] Inert placebo response of pain occurred in 66.6% of patients in group 1 and in 53.8% in group 2. Given the high incidence of placebo response in this series, and in neuropathic patients in general, we propose that the placebo effect is the most likely mechanism for the transient reversal of hypoaesthesia in group 1 patients, in the context of an impressive medical intervention: a nerve block. There is no reason to think that placebo response in those patients should be restricted to the pain and spare other sensory or motor manifestations not based on steady state structural pathology.

Regarding the pathophysiological nature of the hypoaesthesia that improves after inert or active placebo, it is noteworthy that the clinical profile of the patients who displayed it is atypical for peripheral nerve dysfunction and that they lacked peripheral nerve damage. Could secondary pathology in the CNS explain the profile in those atypical patients whose sensory and motor profile cannot be explained peripherally? It has become fashionable to attempt to thus rationalise chronic pain patients with unexplainable "neuropathic" profiles, but the idea rests largely on subjective patient's self reports, or subjective responses to medical interventions not properly controlled for placebo (see critique in Ochoa[36]). Secondary centralisation is most unlikely because in group 1 patients in whom objective neurophysiological tests for central sensory and motor function were applied, the tests were normal at a time that they actively displayed gross negative sensory and motor phenomena. The same finding has been reported by Lacerenza *et al*[37] who concluded: "the concept of centralisation to explain the atypical distribution of sensory-motor positive and negative phenomena in reflex sympathetic dystrophy/causalgia patients is not supported when tested through available clinical neurophysiological methods."

What then is the explanation for the hypoaesthesia that reverses dynamically? Could it be a placebo effect on an organically based negative sensory dysfunction? It cannot be overemphasised that improvement of subjective positive sensory phenomena, such as spontaneous pain or mechanical hyperalgesia in response to inert or active placebo, does not necessarily imply that those manifestations are not the result of organic pathology.[35] Inviting as it is to apply this proviso to explain reversal of negative sensory phenomena, such as cutaneous hypoaesthesia, it is difficult to conceive how a profound sensory deficit, greater than 50%, evolving chronically for months to years, could be purely due to an organically based transmission block of afferent pathways within the CNS, and that such an anomaly would be amenable to placebo reversal. Although it is well known that central mechanisms that normally modulate nociceptor input may decrease intensity of the positive sensory experience of pain,[38] there is no evidence that a

similar mechanism may (or may not) physiologically perpetuate a reversible negative phenomenon of hypoaesthesia. Furthermore, while in operation, this hypothetical block would not affect normal transmission of somatosensory evoked potentials all the way between peripheral nerve and cortical generators.[37] It is even more difficult to conceive a chronic block, caused by a hypothetically occult nerve injury leading to neurapraxia, neurotmesis, or axonotmesis, that might be completely reversed by injection of placebo or lidocaine. It seems much more plausible that the profound hypoaesthesia that significantly reverses in response to placebo or lidocaine injection must be the result of disordered sensory processing at the level of the brain. Therefore, unlike relief by placebo of positive sensory phenomena such as pain, reversal of hypoaesthesia by inert or active placebo should be construed as meaning that such hypoaesthesia is psychogenic in origin. The definition of "psychogenic" as "due to psychic, mental, or emotional factors,"[39] does not incur the false dichotomy that such disorders are unrelated to brain dysfunction.[40 41]

The medical nature of the patient population that displays the neurologically atypical clinical and laboratory profile, and whose psychophysical deficit of sensory (and motor) function is dynamically reversed through a placebo effect, is rationalised by mainstream opinion under the ever fluctuating hypotheses for complex regional painful syndrome I (reflex sympathetic dystrophy[20]). Again, it is noteworthy that in these patients (24 out of 27 in our series) there is no demonstrable structurally based nerve dysfunction. Whereas their clinical picture is atypical for peripheral neuropathic damage, all these patients display explicit evidence of dysfunction of pseudoneurological, psychogenic, origin[42 43]

- Muscle weakness with interrupted wilful upper motor neuron drive, in the absence of pain or dysfunction of motor units (13/15)[5 27 28]
- Cutaneous hypoaesthesia which does not follow nerve trunk or spinal root territories (26/27)[44 45]
- Cutaneous mechanical hyperalgesia which does not follow normal anatomical distribution (19/25)[8]
- Positive evidence of non-organic hypoaesthesia, as for example punctual denial of each tactile stimulus (3/27).

The presence of these neurological phenomena by themselves qualifies the clinical picture of these patients as specific for the diagnosis of "psychogenic regional pain"[45–49] or "pseudoneuropathy,"[11] a psychologically mediated condition ostensibly due to somatisation[50–52] regardless of whether or not a separate diagnosis is attained through psychiatric criteria. Rather than searching for neuropathophysiological abnormalities in the peripheral or central afferent pathways of these patients, psychopathophysiological derangements in areas of the brain serving emotional, volitional, or attentional control must be investigated, as done recently for patients with atypical facial pain by Derbyshire *et al*.[53] If psychologically determined, why should pseudoneuropathy patients mimic neuropathy, while displaying a fairly stereotyped clinical profile? This is because the possible repertoire of clinical manifestations actually or potentially brain controlled in nonvisceral body regions, is limited to changes in colour, temperature, voluntary movement, and subjective sensation. We submit that the phenomenon of reversal of hypoaesthesia by placebo or lidocaine injection constitutes a strong criterion for psychogenicity in patients with seemingly neuropathic chronic pains, and should be tested routinely in atypical cases (CPRS I). This would help rectify traditional mis-classification of these patients into meaningless diagnostic categories that foster iatrogenesis.[54–56] Previous alternative interpretations for this puzzling phenomenon are due for reassessment.

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